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The Coordinated Noninvasive Studies (CNS) Project
Phase One

Judith L. Lauter, Ph.D.

AFOSR 88-0352
University of Arizona
1988-1991

FINAL REPORT
December 1991

APPENDICES

The Coordinated Noninvasive Studies (CNS) Project

Phase One AFOSR 88-0352 FINAL REPORT 12/91

APPENDICES

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Appendix A
Curriculum vitae for Principal Investigator

VITA

Judith L. Lauter, Ph.D.

I. IDENTIFYING INFORMATION

Address: [redacted]
Born: [redacted]
Social Security Number: [redacted]

Teaching Interests: Anatomy and physiology for speech & hearing, Acoustic phonetics and speech perception, Sensory perception, Noninvasive methods for studying the human brain

Research Interests: Natural history of brain asymmetries, Dichotic listening to speech and nonspeech complex sounds, Coordinated noninvasive methods for studying complex sensory function in the same subjects, including study of indvidual differences and processing asymmetries (EPs, qEEG, MEG, MRI/MRS, PET)

II. EDUCATION

B.A. English	University of Michigan	1966
M.A. English	University of Arizona	1968
M.A. Information Science	University of Denver	1971
M.A. Linguistics	Washington University (St. Louis)	1974
Ph.D. Communication Sciences	Washington University (St. Louis)	1979

III. EXPERIENCE

1974-1979 Research Assistant, Central Institute for the Deaf, St. Louis MO
1979-1985 Research Associate, Central Institute for the Deaf, and Assistant Professor of Communication Sciences, Washington University at St. Louis, MO
1985-1988 Associate Research Scientist, Dept. of Speech and Hearing Sciences, University of Arizona, Tucson AZ
1988-1991 CNS Project Director, Institute for Neurogenic Communication Disorders, University of Arizona, Tucson AZ
1991-present Associate Professor, John W. Keys Speech & Hearing Center, University of Oklahoma Health Sciences Center, Oklahoma City OK

IV. PROFESSIONAL ACTIVITIES

Professional Associations:

Acoustical Society of America
American Association for the Advancement of Science
International Society of Phonetic Sciences
Society of Sigma Xi
Society for Neuroscience

Consultantships:

McDonnell Center for the Study of Higher Brain Functions, Washington University at St. Louis (1981-1985)
Journal of Speech and Hearing Research, ad hoc reviewer
Journal of the Acoustical Society of America, ad hoc reviewer
Psychobiology, ad hoc reviewer
Audiology, ad hoc reviewer
Journal of Speech-Language Pathology and Audiology, ad hoc reviewer
NINCDS site visit for U. Minnesota PPG proposal on Communication Disorders, 1983
Collaborator status with Los Alamos National Laboratory: Life Sciences Division, Neural and Biological Sciences Group (initiated April 1987)
PET Steering Committee for University of Arizona
Microcomputer Applications Committee for American Speech-Language-Hearing Ass'n.

InstructionalContributions:

Responsible for the following courses and course components at Washington University in St. Louis:

SpH 401 Anatomy and Physiology for Speech and Hearing
SpH 433 Acoustic Phonetics and Speech Perception [team-taught with I.J.Hirsh]
Diagnostic Audiology: lectures on auditory physiology and central auditory disorders
Psychology of Speech and Language: lectures on aphasia
Psychology of Music: lectures on temporal perception
Basic Sciences course for otolaryngology residents: lectures on auditory anatomy and physiology
Neurological Pathophysiology course for second-semester Washington University School of Medicine students: lectures on auditory function and disorders

Course contributions at University of Arizona:

Neurological Foundations of Psychology (Psych 302): lecture on PET as a window on normal human physiology
Introduction to Biopsychology (Psych 403): lectures on development and noninvasive study of speech & hearing system in humans
Research and Theory in Biopsychology (Psych 520); lecture on modern imaging techniques, including PET-scan
Speech Science (S&H 260): lecture series on methods for studying neurological foundations of speech perception

Courses at University of Oklahoma:
Event-Related Potentials (Comm Disord 6853)

V. RESEARCH ACTIVITIES

Directed studies and thesis committees:

(Washington University, St. Louis):

Discrimination of Multisyllabic Sequences by Young Infants (Roanne Karzon, Ph.D. Dissertation, 1982)

Hypnosis and Its Relationship to Right Hemisphere Processing (Jeffrey Levine, Ph.D. Dissertation, 1983)

Perceptual Attributes of Babbling From Four to Twelve Months (Ginger Kuehn, Ph.D. Dissertation, 1984)

Perceptual Correlates of Spectral Changes in Complex Tones (Punita Singh, Ph.D. Dissertation, 1990)

. (University of Arizona, Tucson)

[All students are S&H unless otherwise noted]

Independent Studies:

Carol Baldwin [Psychology], "Readings in acoustic phonetics" (completed)

Nancy Pearl, "VOT variability: a cross-language study" (completed; paper given at ASA in Anaheim fall 1986; MS submitted)

Fang Ling Lu, "VOT production in Chinese talkers: comparisons between Chinese and English stops" (completed; paper given at ASA in Miami fall 1987; MS in prep)

Julie Petersen, "Readings in auditory physiology as background to studies of auditory CNS asymmetries with PET" (1988)

Master's Projects:

Ron Mack (R. Curlee, Advisor) "Reaction time measures in dysfluents and normals" (1986)

Ph.D. Internships:

Elena Plante (L. Swisher, Advisor) "Regional cerebral blood flow activation asymmetries in human brains during rest and auditory stimulation" (1989)

Ph.D. Dissertations:

Carol Baldwin [Psychology; M. Wetzel, Advisor], "The voice of emotion: acoustic properties of six emotional expressions" (1988)

Janet Lord-Maes [Educational Psychology; S. Mishra, Advisor], "Short latency evoked potentials and intra-individual variability in children" (1988)

Robert Oyler [S&H; N. Matkin, Advisor], "Within-subject variability in the absolute latency of the auditory brainstem response" (1989)

Elena M. Plante [S&H; L. Swisher, Advisor], "Cerebral configurations among the parents and siblings of language-disordered boys" (1990)

Sponsored Projects:

Funded

AFOSR 84-0335	84-85	"Complex sounds"	100%	$71,000
AFOSR 85-0379	85-88	"Dichotic listening..."	100%	307,000
AFOSR 87-0003	86	"PET satellite station"	(equip)	80,500
AFOSR 88-0352	88-91	"CNS Project"	100%	300,000
ASHF/Apple		"CAD tests"	(equip)	15,000

Approved, not funded

NIH (NINCDS)	"Individ. diffs in EPs"	650,000
NIH (NINCDS)	"PET satellite system"	380,000
NIH (NINDS)	"CNS Project"	1,450,000

VI. LECTURES AND PAPERS (Invited and Submitted)

1979

"A speech microscope," (with R Vemula, AM Engebretson, R Monsen) to Acoustical Society of America, Cambridge. Reprinted in JW Wolf & DH Klatt (Eds), Speech Communication Papers; NY: ASA; pp. 71-74.

1980

"Dichotic identification of complex sounds," to Acoustical Society of America, Atlanta. Abstract: J Acoust Soc Amer 67: S100.

1981

"Dichotic listening reconsidered as a type of masking paradigm," to Acoustical Society of America, Ottawa. Abstract: J Acoust Soc Amer 69: S22.

1982

"Contralateral interference and relative ear advantages for event timing in three-tone patterns," to Acoustical Society of America, Chicago. Abstract: J Acoust Soc Amer 71: S47.

"The psychophysics and neurophysiology of hearing," lecture series presented to the Brain Breakfast Club, Washington University Department of Neurology, St. Louis.

"Ear advantages: what are they good for?" to staff of Kresge Hearing Institute of the South, New Orleans.

1983

"Bandwidth of three-element patterns and its effect on relative ear advantages," to Acoustical Society of America, Cincinnati. Abstract: J Acoust Soc Amer 73: S43.

"Human auditory cortex: a preliminary report on studies using positron emission tomography (PET)," (with P Herscovitch and ME Raichle) to Acoustical Society of America, Cincinnati. Abstract: J Acoust Soc Amer 73: S60.

"Cerebral metabolic effects of auditory stimulation," to Brain Breakfast Club, Washington University Department of Neurology, St. Louis.

"Tonotopic organization in human auditory cortex as revealed by regional changes in cerebral blood flow," (with C Formby, P Fox, P Herscovitch, ME Raichle) to XI International Symposium on Cerebral Blood Flow and Metabolism, Paris. Abstract: J Cereb Blood Flow Metab 3: S248-249.

"Dichotic listening and models of the nervous system," to Computer Systems Group, Los Alamos National Laboratory, Los Alamos NM.

"PET and the cortex: the effects of auditory stimulation on cerebral blood flow," to Department of Speech and Hearing Sciences, University of Arizona, Tucson.

1984

"Changes in human regional cerebral blood flow in response to pure tones," to Acoustical Society of America, Norfolk. Abstract: J Acoust Soc Amer 75: S14.

1985

"Individual differences in the perception of frequency changes in three-element sequences," to Acoustical Society of America, Austin. Abstract: J Acoust Soc Amer 77: S36.

"Individual differences in auditory evoked responses: comparisons of between-subject and within-subject variability in brainstem and cortical waveforms," to Acoustical Society of America, Austin. Abstract: J Acoust Soc Amer 77: S65.

"Human auditory central nervous system: visualization of cortical and subcortical centers with regional cerebral blood flow measurements on the PETT-VI," to Acoustical Society of America, Austin. Abstract: J Acoust Soc Amer 77: S94.

"Workshop on Central Auditory Processing: Basic Science Background and Clinical Realities", sponsored by the Speech and Hearing Association of Greater St. Louis.

1986

"Dichotic listening: the good news and the bad news," Speech and Hearing Sciences Colloquium, University of Arizona.

"Individual differences in evoked responses: second report," to Acoustical Society of America, Cleveland. Abstract: J Acoust Soc Amer 79: S5.

"VOT variability: Within-subject and between-subject measurements of stop-consonant production by female talkers of English, Japanese, Navajo, and Spanish" (with N. Pearl), to Acoustical Society of America, Anaheim. Abstract: J Acoust Soc Amer 80: S62.

1987

"Using the PET-scan to study normal human brain function," to Los Alamos National Laboratory, Life Sciences Division, Los Alamos NM, March 1987.

"Individual differences in auditory evoked potentials: middle-latency responses," (with R. Karzon) to Acoustical Society of America, Indianapolis. Abstract: J Acoust Soc Amer 81: S8.

"Human auditory physiology studied with positron emission tomography," (with P. Herscovitch and M.E. Raichle) invited paper to Auditory Pathway: Structure and Function conference, Prague.

"VOT variability in stop-consonant productions by bilingual speakers of English and Mandarin Chinese," (with Fang-Ling Lu) to Acoustical Society of America, Miami. Abstract: J Acoust Soc Amer 82: S115.

"VOT variability in Mandarin Chinese: interactions with tone," (with Fang-Ling Lu) to International Society for Phonetic Sciences, Miami Beach.

1988

"The PET scan as a tool for studying human neurophysiology," to University of Arizona Medical School Neurology Grand Rounds, Tucson AZ.

"Gender differences in the production of vocal emotional expressions" (with Carol M. Baldwin and Peter C. Facciola), to Western Psychological Association, San Francisco CA.

"Windows to the brain," to American Speech-Language-Hearing Foundation Technology Conference, Mesa AZ.

"Toward a taxonomy of vocal expressions of emotion" (with Carol M. Baldwin and Peter C.

Facciola), to Society for Psychotherapy Research, Santa Fe NM.

"Windows to the brain: What contemporary imaging devices can reveal about speech and hearing," University of Wisconsin University Extension Program Communication Disorders all-day Workshop, Madison WI.

"Assessment techniques and what they can tell us," to American Speech-Language-Hearing Association Clinical Neuroscience Conference, Bethesda MD.

"Positron emission tomography as a tool for studying normal human brain function," to University of Tennessee PET Laboratory, Knoxville TN.

"Functional-activation asymmetries in normal humans studied with quantitative EEG (qEEG): first tests in the CNS Project," to Acoustical Society of America, Honolulu HI. Abstract: J Acoust Soc Amer 84: S57.

1989

"Introduction to the new noninvasive techniques, from EPs to PET," to Dept. of Psychiatry, University of Arizona Medical Center, Tucson AZ.

"Windows on the brain: What the new imaging techniques can tell us about speech, language, and hearing," all-day Workshop sponsored by Dept. of Speech & Hearing Sciences, Tucson AZ.

"Comparisons of between- and within-subject variability in repeated-measures auditory brainstem responses (ABRs) in 5-7-year-old children" (with J.M. Lord-Maes), to Acoustical Society of America, Syracuse NY. Abstract: J Acoust Soc Amer 85: S38.

"Global brain asymmetries in regional cerebral blood flow (rCBF) during resting conditions with positron emission tomography (PET): establishing a baseline for experiments on brain asymmetries and complex sounds in the CNS Project" (with E. Plante), to Acoustical Society of America, Syracuse NY. Abstract: J Acoust Soc Amer 85: S69.

"Relevance of studies in normal subjects to clinical applications of PET," to conference on "Clinical PET: When? How? Where?," Knoxville TN.

"Individual differences in ABRs in normal children and adults," (with J. M. Lord-Maes and R.F. Oyler), to American Speech-Language-Hearing Association, St. Louis MO.

"Windows to the brain: a survey of new noninvasive methods," a three-hour short course, presented to American Speech-Language-Hearing Association, St. Louis MO.

"MacCAD: a Macintosh-based program for central auditory diagnostics," in the Building Bridges Project presentation to American Speech-Language-Hearing Association, St. Louis MO.

"Comparisons of between- and within-subject variability in repeated-measures auditory brainstem responses (ABRs) in 10-12-year-old children" (with R.F. Oyler), to Acoustical Society of America, St. Louis MO. Abstract: J Acoust Soc Amer 86: S45.

"Functional organization of normal human auditory central nervous systems observed with multiple noninvasive techniques: Year One of the CNS Project," to Acoustical Society of America, St. Louis MO. Abstract: J Acoust Soc Amer 86: S46.

1990

"Developmental aspects of between- and within-subject relative variability in auditory brainstem responses (ABRs)" (with J.M. Lord-Maes and R.F. Oyler), to Association for Research in Otolaryngology, St. Petersburg Beach FL.

"New brain imaging technologies for studying human communication," invited lecture to the Arizona Speech and Hearing Association, Phoenix AZ.

"PETs I have known: studies of motor and sensory asymmetries in the human brain," invited presentation to staff of Good Samaritan Hospital, Phoenix AZ.

"Noninvasive studies of brain function: a survey of modern technologies," a three-hour short course, presented to New York State Speech and Hearing Association, New York NY.

"Windows on the brain," a three-hour short course, presented in the Van Riper lecture series, Western Michigan University, Kalamazoo MI.

"Thinking vs. feeling: personality type correlates in the production of emotional speech," (with C. Baldwin), to Rocky Mountain Psychological Association, Tucson AZ.

"Repeated-measures auditory brainstem responses (ABRs): comparisons of stability profiles based on different time schedules" (with J. M. Lord-Maes), to Acoustical Society of America, State College PA. Abstract: J Acoust Soc Amer 87: S64.

"Repeated-measures ABRs in multiple sclerosis: Demonstration of a new tool for individual neurological assessment" (with J.M. Lord-Maes), to Acoustical Society of America, San Diego CA. Abstract: J Acoust Soc Amer 88: S18.

"The Coordinated Noninvasive Studies (CNS) Project," to Society of Neuroscience, St. Louis MO.

"MacCAD: A Macintosh program for central auditory diagnosis," to American Speech Language and Hearing Association, Seattle WA.

"Repeated Evoked Potentials (REPs): a new tool for individual neurological assessment," to John Keys Speech & Hearing Center, University of Oklahoma Health Sciences Center, Oklahoma City OK.

1991

"Imaging techniques and auditory processing," to conference on "Central Auditory Processing: A Transdisciplinary View," SUNY Buffalo NY. [chapter In Press]

"Windows on the brain: New imaging methods for studying aspects of the human brain related to speech, language, and hearing," three-hour seminar presented to Oklahoma Speech Language Hearing Association, Oklahoma City OK

"MacCAD, a new Macintosh-based Hypercard program for central auditory diagnostics: Description and preliminary findings," to Acoustical Society of America, Baltimore MD. Abstract: J Acoust Soc Amer 89: 1975.

"MacCAD and REP/ABRs: A new test battery for central auditory dysfunction," to Acoustical Society of America, Baltimore MD. Abstract: J Acoust Soc Amer 89: 1975.

"The Coordinated Noninvasive Studies (CNS) Project," to Third IBRO World Congress of Neuroscience, Montreal Quebec.

"Repeated Evoked Potentials (REPs): a new tool for individual neurological assessment," to Neurology Grand Rounds, University of Oklahoma Health Sciences Center, Oklahoma City OK.

"Functional mapping in the human brain using positron emission tomography," to Neurology Grand Rounds, University of Oklahoma Health Sciences Center, Oklahoma City OK.

"Integrative studies of the human CNS," to XII Biennial Symposium of the International Electric Audiometry Response Study Group, Terme di Comano Italy.

"Central auditory dysfunction: qEEG correlates of individual differences in ear advantages and REP/ABR results," to Acoustical Society of America, Houston TX. Abstract: J Acoust Soc Amer 90: 2292.

"Brain mapping: its relationship to audition," to Oklahoma Health Sciences Center Audiology/Audition Professionals, Oklahoma City OK.

"MacCAD: Central Auditory Diagnostics for the Macintosh," to American Speech Language and Hearing Association, Atlanta GA.

"REP/ABRs and MacCAD: A new battery for central auditory diagnostics," to American Speech Language and Hearing Association, Atlanta GA.

1992

"The effect of click rate on ABR stability measured with the REPs/ABR protocol" (with K. Hawkins and T. Venema), to Acoustical Society of America, Salt Lake City UT.

"Anatomical vs. physiological asymmetries in the auditory cortex of normal subjects studied in the CNS Project" (with E. Plante), to Acoustical Society of America, Salt Lake City UT.

VII. PUBLICATIONS

1979

Vemula, R., Engebretson, A.M., Monsen, R., and Lauter, J.L. A speech microscope. In J.L. Wolf and D.H. Klatt (Eds), Speech communication papers presented at the 97th meeting of the Acoustical Society of America. NY: Acoust Soc Amer; pp. 71-74.

1981

Lauter, J.L. Book review of JM Pickett, The sounds of speech communication [1980]. Ann Otol 90: 302.

1982

Lauter, J.L. Dichotic identification of complex sounds: absolute and relative ear advantages. J Acoust Soc Amer 71: 701-707.

1983

Lauter, J.L. Stimulus characteristics and relative ear advantages: a new look at old data, J Acoust Soc Amer 74: 1-17.

Lauter, J.L. Book review of NJ Lass (Ed.), Speech and language. Advances in basic research and practice [1981]. Volta Review 85: 42-43.

Lauter, J.L. Book review of NJ Lass et al (Eds.), Speech, language, and hearing, vols. 1-3 [1982]. New Engl J Med 307: 900-901.

1984

Lauter, J.L. Auditory system. In A.L. Pearlman and R.C. Collins (Eds.), Neurological pathophysiology, 3d. ed., London: Oxford Univ. Press; pp. 86-109.

Lauter, J.L. Contralateral interference and ear advantages for identification of three-element patterns. Brain and Cognition 3: 259-280.

Levine, J.L., Kurtz, R.L., and Lauter, J.L. Hypnosis and its effect on left and right hemisphere activity. Biol Psychiat 19: 1461-1475.

1985

Lauter, J.L., and Hirsh, I.J. Speech as temporal pattern: a psychoacoustical profile. Speech Communication 4: 41-54.

Lauter, J.L. (Editor) The planning and production of speech: report of the conference. ASHA Report #15.

Lauter, J.L. Respiratory function in speech production by normally-hearing and hearing-impaired talkers: a review. In J.L. Lauter (Ed.), The planning and production of speech: report of the conference. ASHA Report #15.

Lauter, J.L., Herscovitch, P., Formby, C., Raichle, M.E. Tonotopic organization in human auditory cortex revealed by positron emission tomography. Hearing Research 20: 199-205.

Lauter, J.L. Book review of FH Duffy and N Geschwind (Eds.), Dyslexia: a neuroscientific approach to clinical evaluation [1985], and BP Rourke (Ed.), Neuropsychology of learning disabilities [1985]. New Engl J Med 313: 898.

1986

Lauter, J.L., and Loomis, R.L. Individual differences in auditory electric responses: comparisons of between-subject and within-subject variability. I. Absolute latencies of brainstem vertex-positive peaks. Scand Audiol 15: 167-172.

Lauter, J.L. Book review of I. Reinvang, Aphasia and brain organization [1985]. New Engl J Med 315: 268.

1988

Lauter, J.L. and R.L. Loomis. Individual differences in auditory electric responses: comparisons of between-subject and within-subject variability. II. Amplitudes of brainstem vertex-positive peaks. Scand Audiol 17: 87-92.

Lauter, J.L., P. Herscovitch, and M.E. Raichle. Human auditory physiology studied with positron emission tomography. In J. Syka and RB Masterton (Eds.), Auditory Pathway. Plenum: NY; pp. 313-317.

Lauter, J.L. Book review of D. Bowsher, Introduction to the anatomy and physiology of the nervous system [5th ed., Blackwell: Oxford, 1988]; and R. N. Rosenberg and A. E. Harding (Eds), The molecular biology of neurological disease [Butterworths: London, 1988]. New Engl J Med 319: 875-876.

1989

Lauter, J.L. and R.G. Karzon. Individual differences in auditory electric responses: comparisons of between-subject and within-subject variability. III. A replication, and observations on individual vs. group characteristics. Scand Audiol 19: 67-72.

1990

Lauter, J.L. Auditory system. In A.L. Pearlman and R.C. Collins (Eds.), The Neurobiology of Disease. NY: Oxford Univ. Press; pp. 101-123.

Lauter, J.L. and R.G. Karzon. Individual differences in auditory electric responses: comparisons of between-subject and within-subject variability. IV. Latency-variability comparisons in early, middle, and late responses. Scand Audiol. 19: 175-182.

Lauter, J.L. and R.G. Karzon. Individual differences in auditory electric responses: comparisons of between-subject and within-subject variability. V. Amplitude-variability comparisons in early, middle, and late responses. Scand Audiol 19: 201-206.

Oyler, R.F., J.L. Lauter and N.D. Matkin. Intrasubject variability in the absolute latency of the auditory brainstem response. J Amer Acad Aud. 2: 206-213.

In Press

Lauter, J.L. Processing asymmetries for complex sounds: Comparisons between behavioral ear advantages and electrophysiological asymmetries based on quantitative electroencephalography (qEEG). Brain & Cognition.

Lauter, J.L. Visions of the brain: New noninvasive imaging techniques and their applications to the study of human speech and language. In H. Winitz (Ed.), Human Communication and Its Disorders, Vol. V.

Lauter, J.L. Imaging techniques and auditory processing. In J. Katz, N. Stecker, and D. Henderson (Eds.), Central Auditory Processing: A Transdisciplinary View.

Lauter, J.L., and R.F. Oyler. Latency stability of auditory brainstem responses in children aged 10-12 years compared with younger children and adults. Brit J Audiol.

Submitted

Lauter, J.L., N.P. Solomon, and C. Baldwin. Variability of voice-onset-time in nonsense stop-CV productions by speakers of American English: data for nine females and seven males, and preliminary comparisons with productions by female speakers of Japanese, Mandarin Chinese, Mexican Spanish, and Navajo.

Lord-Maes, J.M., and J.L. Lauter. Latency stability of auditory brainstem responses in children aged 5-7 years compared with adults.

Appendix B
CNS Project: meeting presentations and preprint abstracts

1. Meeting presentation texts:

Lauter, J.L. (1988) Functional-activation asymmetries in normal humans studied with quantitative EEG (qEEG): First tests in the CNS Project. Presented to Acoustical Society of America, Honolulu HI, November 1988. Abstract: J Acoust Soc Amer 84: S57.

Lauter, J.L. and E. Plante (1989) Global brain asymmetries in regional cerebral blood flow (rCBF) observed during resting conditions with positron emission tomography (PET): Establishing a baseline for experiments on brain asymmetries and complex sounds in the CNS Project. Presented to Acoustical Society of America, Syracuse NY, May 1989. Abstract: J Acoust Soc Amer 85: S69.

Lauter, J.L. (1989) Functional organization of normal human auditory central nervous systems observed with multiple noninvasive techniques: Year One of the CNS Project. Presented to Acoustical Society of America, St. Louis MO, November 1989. Abstract: J Acoust Soc Amer 86: S46.

Lauter, J.L. (1990) Coordinated Noininvasive Studies (CNS) Project. Presented to the following: Society for Neuroscience, St. Louis MO, October 1990; American Association for the Advancement of Science, Washington DC, February 1991; International Brain Research Organization, Montreal Quebec, August 1991.

2. Related preprint abstracts:

Lauter, J.L. (In press) Processing asymmetries for complex sounds: Comparisons between behavioral ear advantages and electrophysiological asymmetries based on quantitative electroencephalography (qEEG). Brain & Cognition.

Lauter, J.L. (In press) Visions of the brain: New noninvasive imaging techniques and their applications to the study of human speech and language. In H. Winitz (Ed.), Human Communication and Its Disorders, Vol. V.

Lauter, J.L. (In press) Imaging techniques and auditory processing. In J. Katz, N. Stecker, and D. Henderson (Eds.), Central Auditory Processing: A Transdisciplinary View.

Functional-activation asymmetries in normal humans studied with quantitative EEG (qEEG): first tests in the CNS Project. Judith L. Lauter (University of Arizona, Tucson AZ 85721) Presented to ASA, Honolulu, November 1988. Abstract: J Acoust Soc Amer 84: S57.

ABSTRACT

Our work with behaviorally-defined asymmetries such as relative ear advantages has led to the CNS Project, designed to apply noninvasive tech- niques such as psychophysics, EPs, qEEG, MEG, MRI, and PET to study human brain responses during functional activation. Preliminary results of a qEEG test series involving both auditory and hand-movement conditions indicate that qEEG power asymmetry patterns reflect at least two types of asymme- try organization: 1) "side of space," e.g., right-hand movement elicits a power asymmetry favoring the left hemisphere, and v.v; and 2) asymmetries based on "higher-level" principles of organization, e.g., coordination during bilateral hand movement, or differential activation based on the physical characteristics of test sounds. As with behavioral patterns of relative ear advantages, qEEG shows individual differences in detail but group agree- ments in overall patterns of response. To our knowledge, this is the first report of qEEG used in this way for studying functional activation in healthy human subjects, and illustrates its potential usefulness for studying human neurophysiology. [Supported in part by AFOSR]

INTRODUCTION

For more than a century, electroencephalography (EEG) has been employed for studying the human brain, by means of both real-time and averaged forms of scalp-recorded potentials. Spectral analysis of ongoing EEG (quantitative EEG, or qEEG) has provided detailed information supporting research on "cognitive processing," including questions related to cerebral asymmetries (for reviews, cf. Gevins & Schaffer 1980, Gevins 1984, Glass 1984).

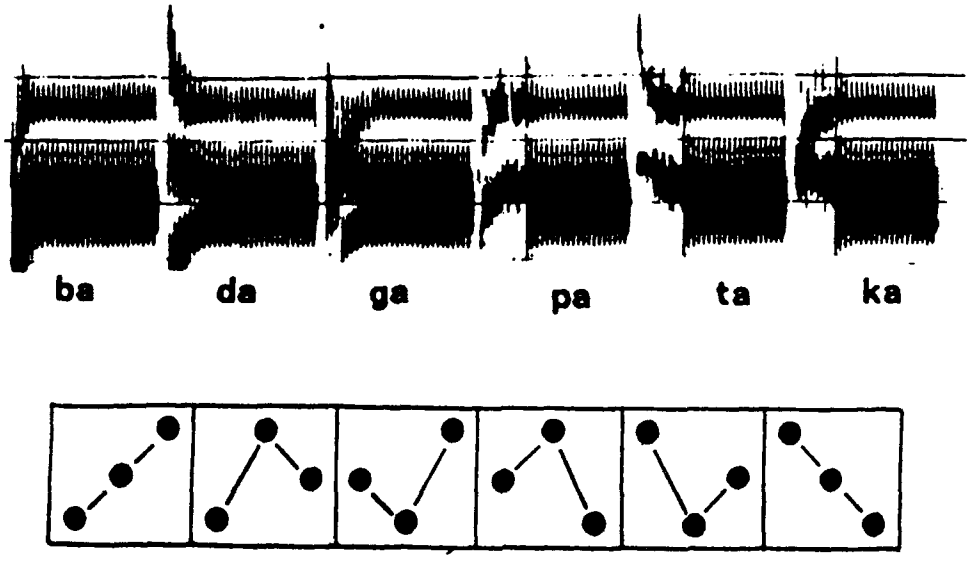
However, surprisingly little is known about the contribution made by "other-than-cognitive" (cf. Gevins 1980) processes to the patterns of EEG activity. Careful study of the effects of relatively simple variables such as rate and level of stimulation, or basic factors related to cerebral asymmetries, such as contralateral vs. ipsilateral representation and influence of stimulus characteristics, may provide primary information regarding brain organization and function, and may even help account for results observed in experiments focused on more "mental" operations.

TESTING

We referred to our research on dichotic listening (Lauter 1982, 1983, 1984) to design an experimental paradigm for use with qEEG. Subjects are pre-tested using

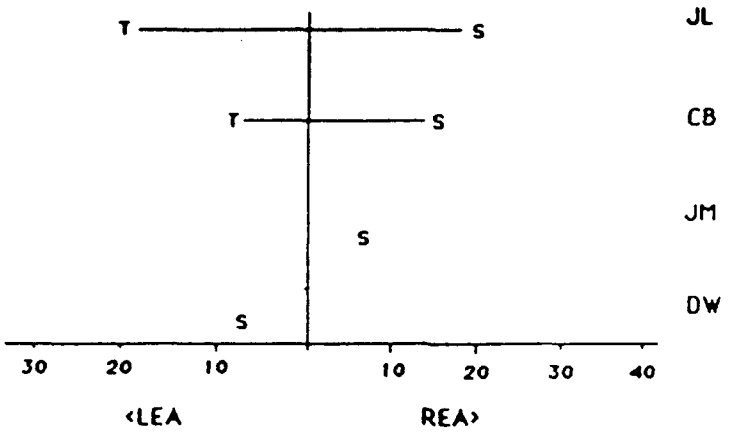
behavioral methods, to familiarize them with monaural and dichotic identification of two sound sets: 1) six synthetic stop consonant-vowel syllables (coded as "S" in the figures below), and 2) six three-note patterns made with three pure tones set at 1440, 1480, and 1520 Hz, with the 25-msec tones set at 200 ms between onsets (coded as "T"). Broad-band spectrograms of the syllables and schematics of the tone patterns are presented in Fig. 1. Identification responses on a total of six 36-trial blocks per sound per subject are collected with ear-of-report alternating from block to block; experimental blocks are approximately 5 min in length.

Fig. 1. Two sets of test sounds: synthetic nonsense stop- consonant-vowel syllables, and three-tone patterns.



Testing for both sound sets requires a total of four hourly sessions per trained subject; different sounds are tested on different days. For two of our subjects, who were trained listeners, complete test series were collected for both sound sets (Subjects JL and CB). The other two subjects (DW and JM) found dichotic identification of the tone patterns quite difficult, and were unable to remain in the experiment long enough to achieve better-than-chance performance with dichotic presentation. The ear advantages obtained for all listeners are displayed in Fig. 2.

Fig. 2 Ear advantages shown by eacn of the 4 subjects on the test sounds; JM and DW were unable to identify the tone patterns when presented dichotically.



After behavioral testing was completed, individuals were scheduled for qEEG testing. Preparation (Fig. 3: color picture of a subject and a qEEG machine, not included for this MS) includes fitting of an electrode cap, with leads connected to a Cadwell Spectrum 32 qEEG system, with capabilities for multi-channel data collection and spectral analysis. Electrodes are placed at 8 locations over each hemisphere, and 5 locations along midline, according to the 10-20 system; potentials at all locations are referenced to linked earlobes. When impedance for each of the leads is less than 8 ohms, testing is begun.

The schedule of conditions is shown in Table I. A time base similar to that used in the behavioral testing is used, with 5 min of EEG collected during each test condition. Note that each test session concludes with a brief set of blocks involving motor activation. Throughout, the subject reclines in a comfortable chair in a quiet, darkened room. Test sounds are played via a stereo cassette recorder through stereo earphones. During monaural stimulus conditions, subjects are told to attend to the ear of input; during dichotic conditions, they are told to attend to the ear targeted for that condition in the same way done for the behavioral tests previously. We do not ask for score-able identification performance during the EEG testing, in order to avoid movement artifacts. Trained subjects report that it is easy to perform this "mock" dichotic listening. The qEEG results suggest that the two trained listeners here were in fact successfully replicating processing patterns used in the behavioral testing.

Table I. Conditions tested per session

1. Control (no activation)
2. Synthetic syllables in left ear
3. Synthetic syllables in right ear
4. Synthetic syllables dichotically, attend to right ear
5. Syllables dichotically, attend to left ear
6. Control
7. Tone patterns in right ear
8. Tone patterns in left ear
9. Tone patterns dichotically, attend to left ear
10. Tone patterns dichotically, attend to right ear
11. Control
12. Preferred hand flexion, 1/sec
13. Opposite hand flexion, 1/sec
14. Bilateral hand flexion, 1/sec
15. Control

DATA ANALYSIS

Data were analyzed off-line. From each 5-min EEG record, 36 2.5-sec artifact-free epochs were selected by eye (cf. Fig. 4: a color figure, showing the EEG waveform display; not included in this MS). The Cadwell Spectrum 32 then averaged the selected epochs, performs spectral analysis according to 4 EEG bandwidths (see Table II), and displayed the results in terms of the parameters shown in Table II. From each table representing each subject tested on each condition, a single number is chosen: 1) for the auditory conditions, the value used is the beta power asymmetry comparing temporal-lobe electrode locations T3 and T4; 2) for the hand-movement conditions, beta power asymmetry comparing F7 vs. F8 is used.

Table II. Sample data table calculated for each test condition, showing values for 4 qEEG parameters by electrode location and bandwidth. (Bandwidth ranges shown at bottom).

Name: Lauter, Judith
Age: 44.0 yrs 8 Epochs: 48
Date: 06/07/88
Time: 10:10:10

Monopolar Raw Measures

		Fp1	Fp2	F7	F8	F3	F4	C3	C4	Fpz	Fz	Cz
Absolute Power (uU²)	Δ	6.2	5.8	4.4	3.9	7.0	6.5	6.1	5.8	6.1	7.6	7.6
	θ	5.9	5.6	4.3	3.5	7.7	7.1	7.5	6.8	5.9	8.4	8.2
	α	8.6	8.2	6.6	5.3	10.3	10.1	15.2	12.0	8.6	11.5	11.4
	β	8.6	8.8	6.2	4.6	11.6	10.2	9.2	8.7	8.4	11.7	9.4
	T	29.4	27.7	21.6	17.5	36.7	34.0	38.1	33.6	29.1	39.4	36.8
Relative Power (%)	Δ	21.1	21.0	20.3	22.6	19.2	19.2	16.0	17.5	21.1	19.4	20.8
	θ	20.3	20.4	20.1	20.2	20.9	20.8	19.7	20.4	20.3	21.3	22.3
	α	29.2	29.7	30.7	30.6	28.1	29.6	39.9	35.9	29.5	29.3	31.2
	β	29.2	28.8	28.8	26.3	31.6	30.2	24.3	26.1	28.9	29.8	25.5
Power Asymmetry (%) [L-R]	Δ	3.1		4.9		3.5		1.8				
	θ	2.6		10.1		4.0		4.4				
	α	2.0		10.5		1.1		11.4				
	β	3.6		14.8		6.0		2.6				
Coherence (%)	Δ	95.1		48.1		93.1		88.3				
	θ	92.8		37.3		89.0		77.3				
	α	95.0		42.2		86.5		42.6				
	β	91.5		48.4		79.5		32.7				

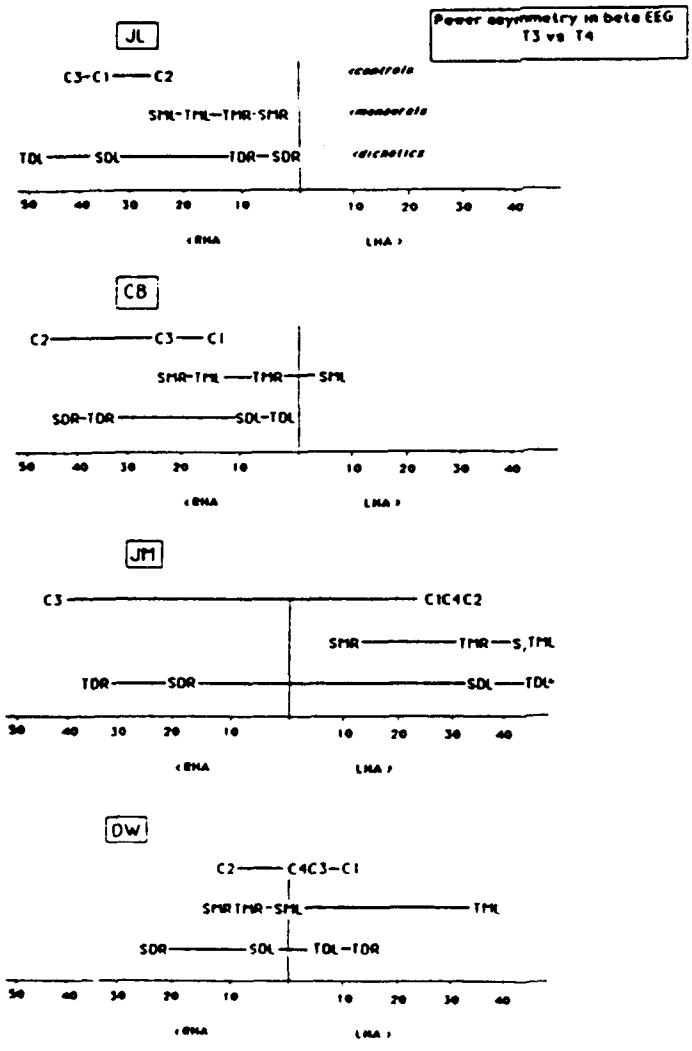
		T3	T4	T5	T6	P3	P4	O1	O2	Pz	Oz
Absolute Power (uU²)	Δ	2.9	2.8	3.1	2.6	5.2	4.9	3.8	2.7	6.1	2.7
	θ	3.5	3.0	3.8	2.7	6.0	5.6	3.2	2.8	6.6	2.9
	α	8.4	7.0	10.0	5.9	13.3	10.6	6.5	6.5	11.0	5.8
	β	4.7	9.7	7.4	4.6	8.4	7.1	7.4	6.1	8.2	5.8
	T	19.6	22.7	24.4	15.8	33.0	28.2	21.1	18.3	32.8	17.3
Relative Power (%)	Δ	14.8	12.6	12.7	16.4	15.8	17.5	18.3	14.8	18.7	15.6
	θ	18.1	13.4	15.6	17.3	18.1	19.8	15.3	15.7	20.1	16.7
	α	42.9	31.0	41.0	37.1	40.4	37.5	31.0	35.9	35.9	33.6
	β	24.1	42.8	30.5	28.9	25.5	25.0	35.1	33.4	25.0	34.0
Power Asymmetry (%) [L-R]	Δ	0.4		0.8		2.7		17.7			
	θ	7.5		16.1		3.3		5.8			
	α	0.9		25.9		11.3		-0.1			
	β	-34.4		23.6		8.6		9.6			
Coherence (%)	Δ	35.3		63.3		90.5		83.3			
	θ	12.9		44.9		83.4		87.6			
	α	16.4		15.3		66.3		75.6			
	β	12.2		5.9		60.4		67.3			

Δ = 1.5 - 3.5 Hz
θ = 3.5 - 7.5 Hz
α = 7.5 - 12.5 Hz
β = 12.5 - 20 Hz

RESULTS

Results for the auditory conditions are presented in Fig. 5, using a format adapted from the EA graph of Fig. 2. The four panels of Fig. 5 present T3/T4 beta-asymmetry values for 4 individual subjects tested on 3 control and 8 auditory conditions. Data for control, monaural, and dichotic conditions are plotted on separate rows. Behavioral ear advantages for each subject for the 2 sound sets are indicated at the top of each qEEG plot. The qEEG results indicate evidence of 2 types of asymmetry: 1) one based on "side of space" in that attention to right vs. left ear results in opposite asymmetries; and 2) an asymmetry based on type of sound, in that attention to syllables vs. tones results in opposite asymmetries. There are also interactions between the two types of asymmetry, such that right-ear syllables tend to evoke one extreme of asymmetry and left-ear tones the opposite extreme.

Fig. 5 qEEG asymmetries: Complex sounds



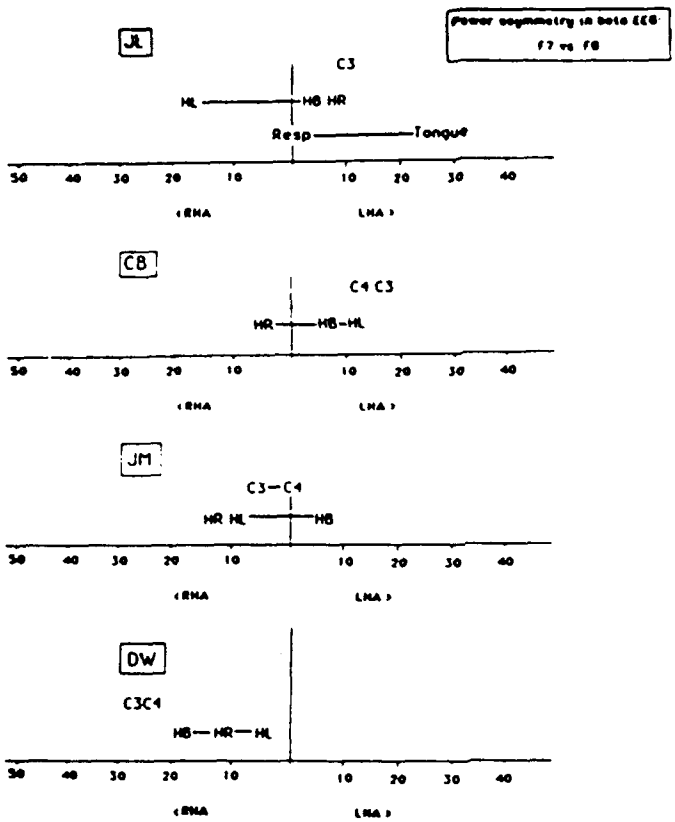
Based on the results for the subjects shown in Fig. 5, it cannot be said that the observed asymmetries always reflect predominantly contralateral activation, although this would be the predicted result. Only Subject JL shows a trend toward the expected "contralateral effect," with greater right-hemisphere asymmetries (RHA) for left-ear input/attention, and vice versa. Notice, however, that even for JL, the patterns of asymmetry are articulated in terms of modulations of RHA-- *none of the auditory conditions shows an actual left-hemisphere asymmetry for this subject.* This observation is in contrast to the behavioral results shown in Fig. 2, where the syllables evoked a 20% right-ear advantage, and the tones evoked a 20% left-ear advantage. The qEEG asymmetries suggest that JL's behavioral results may indeed reflect changes in *relative* hemisphere activation, but these are changes which occur in the context of a continuing processing predominance favoring the right hemisphere.

All of the other subjects show what must be interpreted as "ipsilateral" patterns of activation, with right-ear input/attention and syllables evoking a greater RHA than left-ear input/attention and tones. No known characteristic of these subjects accounts for this finding; JL, CB, and JM are all female and both personally and familial right-handed; DW is a personally left-handed, familial right-handed male. Note also that these "ispilateral" qEEG patterns are not always in agreement with the behavioral EA results shown in Fig. 2: CB's behavioral EAs are REA for syllables and LEA for tones, yet her qEEG patterns show greater RHA with right-ear attention to both types of dichotic presentation.

Given this puzzling result, however, the internal consistency of the asymmetry patterns is quite good: right ear vs. left ear input/attention, and syllables vs. tones tend to show opposite asymmetries, and the interaction between ear and type of sound is similar to that seen for JL: syllables tend to evoke asymmetries in the same direction as right-ear input/attention, and tones evoke asymmetries in the same direction as left-ear input/attention.

Fig. 6 presents qEEG results for the motor activation conditions for all 4 subjects, in terms of beta power asymmery comparing electrode locations F7/F8. Note that JL shows a clear contralateral activation pattern, while the other three are consistent in their "ispilateral" pattern. JL and CB showed resemblances between bilateral hand movement and movement of one of the other hands (R for JL, L for CB). Failure of the other two Ss to show such a match may be due to the high levels of artifact present throughout their records during these conditions, which were tested late in each session. In the future, we plan to test the somewhat fatiguing hand-flexion conditions first, while the subjects are fresh.

Fig. 6 qEEG asymmetries: Motor control

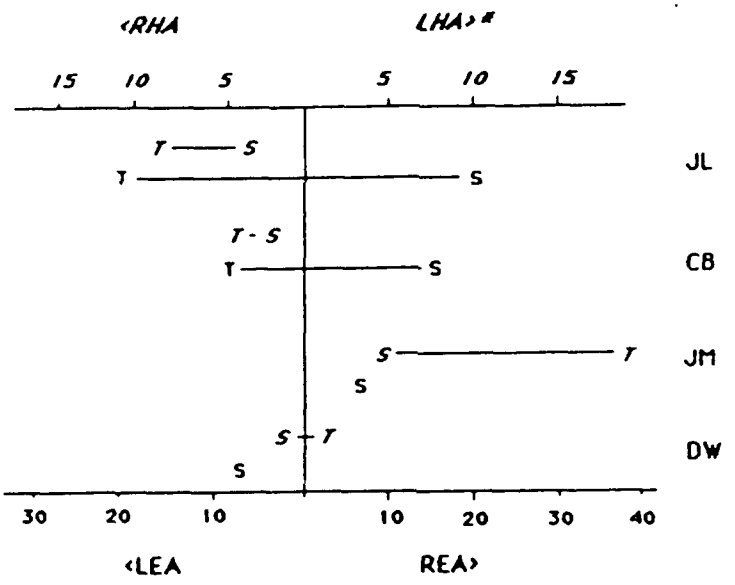


CONCLUSIONS

Although a number of questions are generated by these data, we believe that as preliminary findings, the results are encouraging regarding the potential usefulness of qEEG as a tool for studying cerebral responses to fairly simple stimulus and task combinations, and indicate that "cognitive" processes are not the only phenomena that might be usefully studied using qEEG.

Comparisons between the EAs tested behaviorally and "hemisphere advantages" (HAs) calculated for the qEEG results, for each subject, are shown in Fig. 7. An example of the procedure used to calculate the qEEG HAs is given below the figure.

Fig. 7. Comparisons between behaviorally-determined ear advantages (lower abscissa: non-italics) and qEEG hemisphere advantages (upper abscissa: italics).



*calculated as shown in example below for JL

1	SDR	5.2	5.5	3 RHA
2	SDL	5.0	10.3	5.3 RHA
3				mean=2.8 RHA
4	TDL	6.4	20.7	14.3 RHA
5	TDR	9.4	11.8	2.4 RHA
				mean=8.4RHA

The degree of individual differences seen in all of these results suggests that more subjects need to be tested, particularly if we are to understand the significance of the "ipsilateral" pattern of activation shown by 3 of the 4 subjects. Future designs will also require all subjects to complete behavioral testing on all sounds before testing with qEEG.

We expect that some of these puzzles will be resolved as future subjects undergo in-depth testing in our Coordinated Noninvasive Studies (CNS) Project. In this Project, subjects will first be tested behaviorally to establish each individual's ear advantages on

3 types of sounds, and then will be tested on a variety of noninvasive devices in order to observe anatomical and physiological brain asymmetries (Fig. 8: a color figure not included in this MS). Tests will include: Magnetic Resonance Imaging (MRI), Evoked Potentials (EPs--specifically, Auditory Brainstem Responses ABRs), qEEG, Magnetoencephalography (MEG), and Positron Emission Tomography (PET). Procedures will be based on our previous work with some of these devices (EPs: Lauter & Loomis 1986; in press; PET: Lauter et al 1985; 1988). During testing with each physiological device, subjects will be stimulated on separate test runs with each of the 3 sound sets. Patterns of asymmetries in measurements with the different noninvasive devices will be compared with each other, and with the behavioral asymmetries shown by the same subject (Fig. 9: a color figure not in this MS).

It is expected that the "view" of the brain available with each of the approaches will be most interpretable when considered in the context of the results on all the devices. The immediate goal of the CNS Project is to determine the degree of match between patterns of asymmetry tested behaviorally and patterns of asymmetry with regard to the same stimuli when tested using physiological methods. The ultimate goal of the Project is to take the first steps toward articulating a bridge between brain and behavior based on the new noninvasive methods, demonstrating the value of these new approaches for studying the brain by illustrating at least one way in which they may serve as the tools in a "new neuroscience," based on noninvasive methods and focused on study of the human brain.

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Global brain asymmetries in regional cerebral blood flow (rCBF) observed during resting conditions with positron emission tomography (PET): establishing a baseline for experiments on brain asymmetries and complex sounds in the CNS Project. Judith L. Lauter and Elena Plante (Speech and Hearing Sciences, University of Arizona, Tucson AZ 85721) Presented to Acoustical Society of America, Syracuse NY, May 1989 [Abstract: J Acoust Soc Amer 85: S69]

ABSTRACT: During 1981-1985, the first author and colleagues at the Mallinckrodt Institute of Radiology at Washington University in St. Louis collected a series of 29 PET-scan studies of the brains of 16 normal young-adult subjects using the PETT VI and intravenous oxygen-15 to test each subject in multiple 40-sec scans, comparing rCBF topography during session-initial and session-final control scans, and under a variety of auditory stimulation conditions. We are currently measuring global hemispheric rCBF in all control scans in this library. Results will be presented for work to date, detailing between- and within-subject comparisons, including patterns of within- and between-session replications. These measures will provide a baseline for our Coordinated Noninvasive Studies (CNS) Project, in which subjects first examined behaviorally for processing asymmetries (e.g., ear advantages), are then tested with PET to determine the degree of correlation between behavioral and physiological asymmetries. [Work supported by AFOSR.]

Interest in the details of human brain function has long been frustrated by the inadequacy of neurobiological experimental techniques. However, a number of new noninvasive devices provide dramatically improved temporal and spatial resolution, which are basic requirements if we are to make use of these new tools to pursue "human neuroscience" in a sophisticated way.

Over the last few years we have reported to this Society and published reports (cf. references 1-7) of results using one of these approaches, positron emission tomography (PET), conducted using the PETT VI scanner [SLIDE ONE--not in this reprint], to study responses in normal human brains to a variety of auditory stimulations. It is often the case that analysis of regional changes in brain activity during stimulation reveals graded response asymmetries. For example, the next slide [SLIDE TWO--not in this reprint; published in ref. # 7] illustrates simultaneous activation at several levels along the auditory neuraxis, while the subject was listening to binaural synthetic stop-CV syllables. Differences in the degree of asymmetry at four levels are apparent: 1) a clear asymmetry, occurring at a high level, perhaps in language areas, 2) moderate asymmetry in primary auditory cortex, 3) a large but symmetrical response in posterior thalamus, and 4) response at the midline in the most caudal slice, perhaps auditory midbrain, where PET resolution

does not allow an examination of side-to-side differences.

In order to be able to interpret the apparent symmetries and asymmetries of regional responses such as these, we need to know more about brain asymmetries occurring at a more global level, which may affect regional activity during both control and stimulation conditions.

We are currently examining our PET library of 29 studies using auditory stimulation in normal young adults to document patterns of global brain asymmetries. The first two questions for this project include: [SLIDE THREE]:

1) Does PET show any global brain asymmetries during "resting" conditions?
2) Do these asymmetries change in either direction or magnitude over time?

To date, we have completed analysis for one-half the "resting" or control scans in our series, representing 13 subjects tested in 16 sessions. Control scans are those in which the subject lies quietly, with eyes closed and covered, in a darkened room with ears plugged, with no auditory stimulation other than the low-level ambient sound of equipment used for the scanning. Sessions typically begin and end with control scans, with a range of from 1.5 to 4 hours separating the two scans.

[SLIDE FOUR--not in this reprint] Each of six slices for each scan is displayed in isolation, as shown here, and a cursor used to outline each half-slice, along the midline, located based on the midline-artifact "hot spots," shown in white, and around the entire lateral edge of each slice. Image-analysis software then provides statistics for each half-slice, as activity mean and standard deviation The half-slice values are summed to yield totals for global right- and left-hemisphere activity, which are then subtracted to obtain a measure of hemisphere asymmetry in terms of both magnitude (e.g., units of cerebral blood flow) and direction, i.e., either no asymmetry, or favoring the right, or the left hemisphere.

Results for 13 subjects tested in 16 sessions are shown in the next slide [SLIDE FIVE]. For both control scan #1 (filled bars) and control scan #2 (open bars), every subject in every session, regardless of handedness, yielded a resting asymmetry which in absolute numbers favors the right hemisphere. The majority of these asymmetries are significant; those few sessions where hemispheric values were not significantly different are indicated by a dot at the base of the bar. Other researchers have found similar resting asymmetries favoring the right hemisphere (e.g., ref. #8).

There are also changes here in the magnitude of asymmetry from scan to scan, which can be described in terms of three categories of change:

1) A single subject (ShB 349), with significant asymmetries during both control scans, showed no change in the magnitude of asymmetry over time.

2) Eleven of the 16 sessions involved a decrease in the magnitude of asymmetry over time. Examples are JL106 and 110, and StB 324 and 347: both pairs of sessions are examples of cases where the same subject shows good replicability of asymmetry on re-test.

3) The third category was represented by only 4 of the 16 sessons, indicated by an arrow next to the session number--in these sessions, the magnitude of the right-hemisphere advantage in activity level asymmetry actually increased over time.

These resting right-hemisphere activity advantages can be seen at the level of individual slices, as well. [SLIDE SIX] This slide presents slice-by-slice asymmetry data for three subjects, who represent the three categories of asymmetry change discussed for the previous slide: no change in asymmetry over time (P349), a decrease in right-hemisphere advantage from control 1 to control 2 (P253), and an increase in the right-hemisphere advantage over time (P304), a change which is most dramatic for this subject's slice #3, which actually had a left-hemisphere activity advantage during control #1.

The slice-by-slice consistency of the patterns of asymmetry change led us to examine changes in actual activity levels from the first to the second control scan in all subjects. [SLIDE SEVEN] Here are data for the same three subjects, representing brain activity, expressed either as cerebral blood flow or tissue counts, as a function of brain slice, with hemisphere and time as parameters.

A clear pattern emerges from this type of analysis, indicating a direct relation between changes in overall brain activity over time, and changes in the magnitude of the right-hemisphere advantage over time, where: 1) no change in overall activity is matched with no change in magnitude of asymmetry , 2) decrease in overall flow is associated with decrease in the right-hemisphere advantage, and 3) increase in overall flow is associated with an increase in right-hemisphere advantage.

Although our goal in these studies was to describe resting brain asymmetries, without regard to any type of activation protocol, we may have unwittingly included in our "resting" scans a type of activation--in this case, related to level of anxiety. In the past, many PET researchers (e.g., reference 9) have reported that anxiety levels in test subjects are directly associated with levels of global blood flow, with most subjects being more

anxious, with higher global activity, toward the beginning of testing, and a minority becoming more uncomfortable, with higher blood flows, toward the end of testing.

It is possible that our subjects are providing yet another example of changing levels of anxiety over a test session, associated with changes in ovarall blood flow. However, to our knowledge, no previous observations have been made in normals of the association between anxiety, increased global blood flow, and increased magnitude of the right-hemisphere advantage in global activity. The only related PET data is for individuals with panic disorder, studied by Eric Reiman at St. Louis (cf. references 10, 11). These individuals were reported to have right-hemisphere advantages in regional blood flow, which were enhanced compared to normals, even under resting conditions, and which were affected by overall increases in blood flow during elicited anxiety episodes.

The results reported here regarding global brain asymmetries in normal brains will be extended as we continue to conduct similar measurements of images generated during stimulation as well as control scans. The findings will provide a background for interpreting data generated in the Coordinated Noninvasive Studies (CNS) Project, [SLIDE EIGHT--not in this reprint] where subjects are initially tested using behavioral methods, and then examined using a variety of noninvasive techniques, including MRI for anatomy, and Evoked Potentials, quantitative EEG, MEG, and PET for physiology. Except for evoked potentials, physiological testing is conducted during stimulation with the same stimuli tested behaviorally. One initial Project goal is to determine the nature of brain asymmetries revealed by each noninvasive method, as well as the degree of correlation between findings on each of the devices and behaviorally-defined performance.

[SLIDE OFF] Our current findings on normal brain asymmetries during resting conditions observed with PET highlight the importance of establishing a definition of "baseline" for physiological studies of the normal human brain. When conducting this type of testing, it may be important to consider the possibility that the central nervous system behaves as a Gestalt, and that the reactivity of the part is dependent on and can only be interpreted in the context of the status of the whole.

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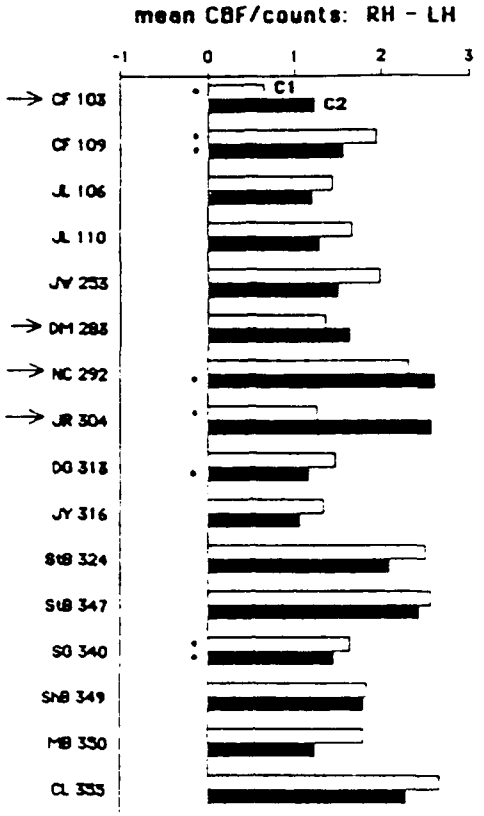
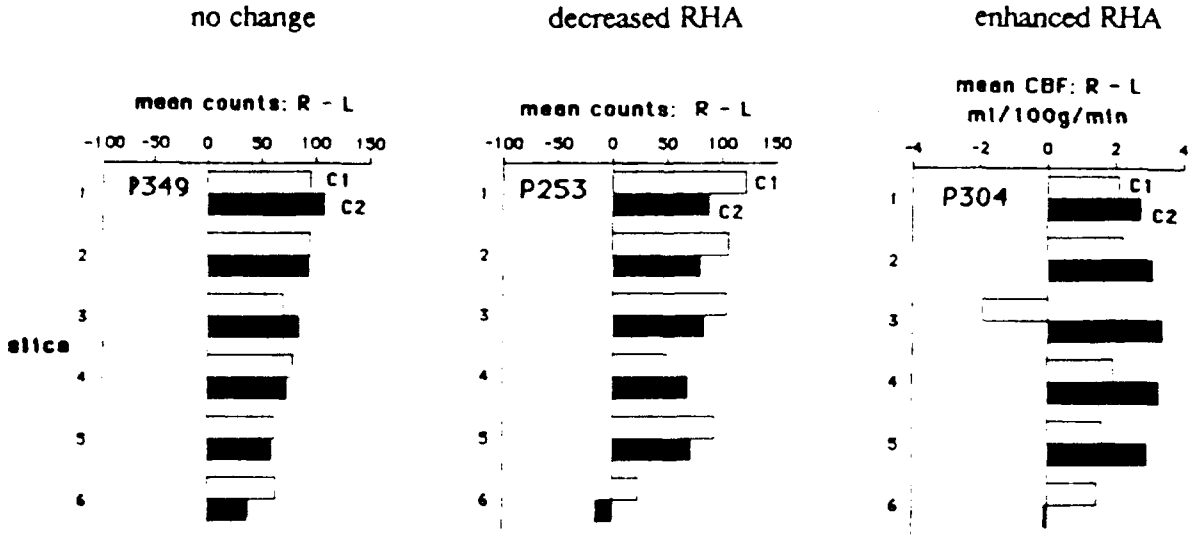
(5)

Global brain asymmetries in two control scans per session

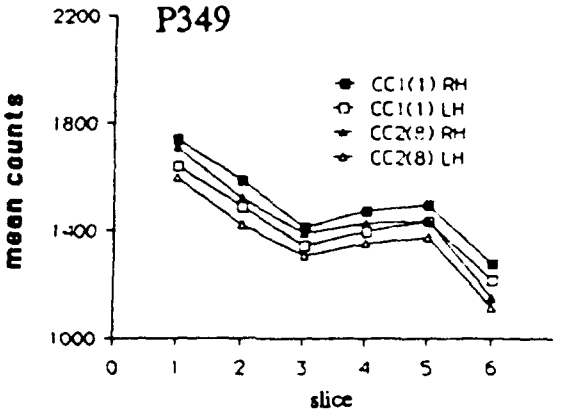


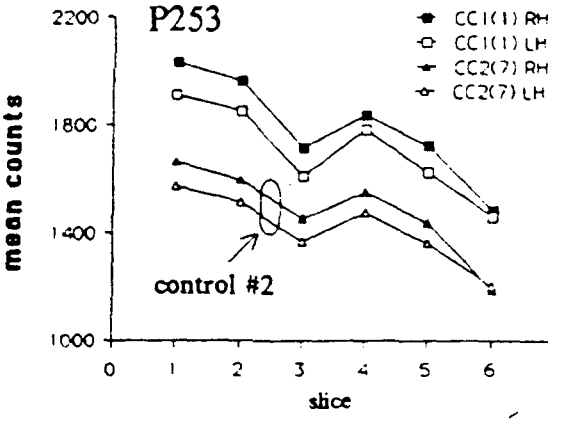
(6)

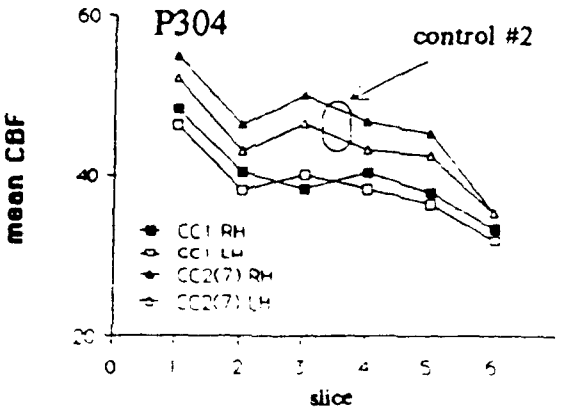
Slice-by-slice asymmetry control #1 vs. control #2



Slice-by-slice flow change over time







Functional organization of normal human auditory central nervous systems observed with multiple noninvasive techniques: Year One of the CNS Project. Judith L. Lauter (Dept. of Speech & Hearing Sciences, University of Arizona, Tucson, AZ 85721). Abstract: J. Acoust. Soc. Amer. 86: S46. (Presented to Acoustical Society of America, St. Louis MO, November 1989)

ABSTRACT

The Coordinated Noninvasive Studies (CNS) Project is designed to bring together a variety of noninvasive methods for studying living brains in order to demonstrate the feasibility of a "human neuroscience" paradigm based on a combination of behavioral testing with noninvasive neuroanatomical and neurophysiological examinations of the same individuals. Initial Project focus is on brain asymmetries related to complex-sound processing. We will present preliminary results on subjects studied to date, documenting: 1) behavioral asymmetries expressed in terms of relative ear advantages, 2) individual differences in anatomical (MRI) asymmetries, 3) patterns of physiological "resting asymmetries," and processing asymmetries observed during auditory stimulation (qEEG, PET), 4) the degree of within-subject consistency of asymmetry direction and magnitude observed with several noninvasive methods (MRI, EPs, qEEG, etc.), and 5) the coincidence of auditory-system asymmetry descriptions based on behavioral vs. neuroanatomico-physiological measurements.
[Work supported by AFOSR]

INTRODUCTION

One of the oldest topics of scientific interest is the relation between brain and behavior--how does the "jelly and water" of the nervous system work to accomplish the complex skills and capabilities shown in the everyday behavior we observe in all animals, and which we too often take for granted in ourselves?

Brain science over the last forty years has been dominated by a single technique, that of single-unit electrophysiology, which has spawned thousands of research papers. However, readers of that literature, and even many of those contributing to it, are becoming increasingly frustrated by the difficulty of using its findings to understand behavior. In spite of the technological brilliance and mathematical complexity of this research, it is becoming more and more obvious that the deeper one delves into the trees, the less can be seen of the forest.

Fortuitously enough, in the last five to ten years, a number of new techniques for studying the brain have become available (Fig. 1)--some of them are new versions of old approaches--such as new methods for collecting and analyzing evoked potentials, while others are entirely new, such as MRI and MEG. Also, because these devices are noninvasive, we are finally able to study the living healthy human brain in quite astounding detail. The different devices represent a range of spatial and temporal resolutions, which can be characterized as bridging between the "whole organism response" of behavior at one end, and systems-level organization in the brain, at the other. The next slide (Fig. 2) illustrates this for spatial resolution, with a number of noninvasive devices arranged in what amounts to levels of focus of a "microscope," where order-of-magnitude changes represent successive steps from behavior down toward details of brain organization on the order of cortical columns.
And, although the spatial resolution already available in these machines may seem "crude" compared with

microelectrodes, observing the brai.. 5 mm at a time rather than one cell at a time may bring us much closer much faster to an understanding of the brain mechanisms underlying human behavior.

As this figure suggests, it is possible that one very powerful use of these new noninvasive techniques for studying the relations between brain and behavior might be to combine them, in a test-battery approach, taking advantage of the complementary nature of their differing resolutions in order to get a more complete representation of the brain.

The Coordinated Noninvasive Studies (CNS) Project (Fig. 3) is designed to take advantage of the complementarity of several of the devices. The Project uses human subjects exclusively, tested in nested repeated-measures designs, i.e., each individual is tested under several stimulus conditions using each of a number of different techniques. We start with each subject by establishing a behavioral "anchor"--a detail of behavior which can be quantified using psychophysical test methods--and then collect anatomical and physiological data to determine whether, when we look inside the same subject's brain, we can find structural and/or functional details that correspond to the pattern of individual performance tested behaviorally. Eventually, we hope to formulate hypotheses that those details of brain organization account for the behavior.

One challenge involved in such an approach is defining questions which can be answered in comparable ways by all the devices. One of my own long-standing interests in brain organization has to do with functional asymmetries--and as it happens, all of these devices are admirably suited for studying asymmetries, which they now make it possible to examine in detail whether in terms of behavior, brain anatomy, or brain physiology.

The first type of functional asymmetry we are studying is related to ear advantages for complex sounds. In our dichotic-listening experiments (Lauter 1982, 1983, 1984), we have found that although there are clear individual differences in ear advantages for certain sounds, these differences can be comprehended in terms of patterns of "relative ear advantages"--which are the same from subject to subject. The next three slides (Fig. 4--not in this handout; for examples, cf. citations given above] presents ear-advantage data for a number of subjects tested on synthetic stop-CV syllables and slow tone patterns, illustrating these characteristics. Some subjects show a right-ear ear advantage (REA) for both sound sets, others show divided differences (i.e., REA for one, LEA for the other), and others show left-ear advantages for both. In spite of these individual differences, the majority of the subjects have an ear advantage for the syllables that is "rightward" of the ear advantage for the tones. The only exceptions are the occasional subjects from left-handed families (last two in these figures), who show mirror-image functions. With the CNS Project, we are addressing the question of whether we can observe details of brain structure and function which correspond to these two characteristics of behavioral auditory asymmetries: individual differences in absolute values, but individual agreements in the patterns of relative asymmetry.

METHODS

Each subject undergoes a series of tests (Fig. 5): first, a questionnaire-based sidedness rating (Harris 1974) and audiogram; second, dichotic-listening testing for the two sound sets, until at least 432 trials per ear of report per sound set are collected. During this test series, which may take two or more weeks, the subject is scheduled for an MRI brain scan, for measuring anatomical asymmetries in auditory cortex (procedures described in Plante et al, In Press). During this time the subject is also started on a brainstem EP series, consisting of 4

weekly sessions. The brainstem data are analyzed using a method we have developed for describing asymmetries in the stability of the amplitude of ABR peak III (described in paper R10 earlier in this session--Oyler & Lauter 1989--and in Lauter & Loomis 1986, 1988; Lord-Maes & Lauter 1989; Lauter & Karzon In preparation).

After the dichotic-listening tests are complete, and the subject is well-trained in identifying tokens included in the two sound sets, whether played monaurally or dichotically, the qEEG session is scheduled. In this session, we collect 5 minutes for each of 15 test conditions, which include monaural and dichotic presentation of both sound sets, with left- and right-ear conditions, as well as spaced resting conditions (cf. Lauter 1988).

Next the subject is scheduled for a PET session, in which we test a subset of seven of the conditions tested with qEEG: dichotic right- and left-ear conditions for each sound set, and initial, mid-way, and final resting scans. Guidelines for PET testing are those established in our earlier research, much of which has been reported to this Society (published in Lauter et al 1985a; Lauter et al 1988). Finally, an MEG session is conducted, testing the same stimulation conditions as with PET.

Today I will show you results for four subjects, for the first five tests shown here. We do not yet have PET or MEG data for these individuals.

A second challenge to the type of testing represented by the CNS Project is how to represent the data in a way that will illustrate the degree of correspondence between behavioral and anatomical/physiological asymmetries, as well as the "internal consistency" of the various brain measures. We are displaying the data using the same type of graph used in our ear-advantage experiments (Fig. 6). **Please note that the data shown here are for a hypothetical subject. ** The dimension of asymmetry is shown as an abscissa across the top, increasing left-hemisphere advantage (LHA) indicated toward the left, increasing right-hemisphere advantage (RHA) toward the right. Results from each of the tests are plotted on a separate row along this dimension, to create a total profile for each subject. Behavioral ear advantages are plotted as though they are expressions of the contralateral hemisphere (REAs are show as though they represent LHAs), and a line indicating discontinuity (the skull) divides the behavioral data from the anatomical and physiological hemisphere advantages, plotted in order of increasing spatial resolution, from the crudest, qEEG, at the top, to the finest, MEG, below. Below the cortical measures is a place for indicating the degree of asymmetry which PET may show in posterior thalamus. Across another discontinuity (i.e., as we enter the brainstem) are results from our repeated-measures EP test of brainstem function, with ear advantage plotted as pointing to the contralateral hemisphere.

RESULTS

Actual data for our first subject JL are shown in the next slide (Fig. 7). This is a female, both personal and familial right-handed. She has split ear advantages, REA (presumed left-hemisphere advantage) for the tones, LEA for the syllables. Her resting qEEG shows a strong right-hemisphere advantage in absolute beta-bandwidth power at the auditory-cortex electrode locations (T3/4), and this direction of asymmetry is maintained when she is tested with each of the sound sets. Thus there appears to be a lack of correspondence between the behavioral and qEEG asymmetries: EAs split between REA and LEA, but RHA for both qEEG tests. Notice, however, that even though both activation qEEG values favor the right hemisphere, in relative terms, they are in the same order left to right as the behavioral scores: as the EA for the syllables is to the left of the EA for the tones, qEEG asymmetry for the syllables is to the left of the qEEG asymmetry for the tones. Thus there is a very good match in relative terms, between the behavioral ear-advantage values and the qEEG values for the two sound sets.

The MRI results include a measure of whole-hemisphere volume (the dotted box) as well as a measure of asymmetry in "periSylvian" areas (the cross-hatched bar). In this subject, both volume measures favor the right hemisphere. [The most common finding is a larger right hemisphere combined with a larger left-sided periSylvian region--cf. Plante et al In Press.]

The brainstem asymmetry measure favors the left ear. This seems to be consistent with the generally right-hemisphere favoring of some of the other measures: hemisphere volume, resting qEEG, and activation qEEG, suggesting a "left-ear/right-hemisphere" biased auditory system.

Data for the second subject AB are shown in the next slide (Fig. 8). This is another personal-right, familial-right-handed female. Instead of JL's split EAs, AB gave ear advantages in the same direction for the two sound sets, both LEAs--but note that the values have the same relative distribution as for JL: EA for the syllables to the left of the EA for the tones.

Again in contrast to JL, this subject's qEEG measures all favored the LEFT hemisphere--under resting as well as during both activation conditions. Still, the match we saw in JL's data between the relative asymmetries for the two sound sets occurs here: EA for syllables to the left of EA for tones, and qEEG asymmetry for syllables to the left of the asymmetry for tones.

In the MRI measures, AB had a larger right hemisphere (like JL), but unlike JL, her periSylvian region is larger on the left. This particular contrast between the two subjects provides the first detail which may be a clue to a correspondence between the anatomical and physiological data, namely, that the qEEG values are asymmetrical in the same direction as the periSylvian volume measures--if we look back for this feature in JL's data, we see that the same is true for her.

Now, back to AB again, and her brainstem asymmetry: like JL, hers favors the left ear. Unlike JL, this does not "point to" a contralateral resting qEEG asymmetry--rather, it is ipsilateral to the direction of resting qEEG hemisphere advantage. This suggests that perhaps there is no relation between this particular measure of brainstem asymmetry and the qEEG measures, after all.

The next subject (Fig. 9) is ES, who is personally ambidextrous, with a left-handed daughter. (We are currently collecting data on the daughter.) ES's data are in some ways to similar to those we just saw for AB: LEAs for both sound sets, with a relative distribution matching both JL's and AB's: syllables' EA to the left of that for tones. In fact, ES's performance on both sound sets was fairly poor, which restricted the dynamic range for EAs. Also like AB, her qEEG measures show a left-hemisphere advantage, both for resting and activation conditions.

Her MRI measures showed a slightly larger left hemisphere. As for her periSylvian data, they show--as we would now predict based on the qEEG values--a larger on the left, matching the qEEG LHA.

ES is the first subject to show a REA in the brainstem measure. Based on the data available for these subjects, we cannot see any significance of this distinction.

Finally, the fourth subject SJ (Fig. 10) is the first to be both personally and familial left-handed. She is also the first to show a behavioral REA for both sound sets, and a relative EA distribution that is opposite to that for the other three subjects: her EA for the syllables is to the right of the EA for the tones.

This same relative-asymmetry pattern is repeated in her qEEG activation data, against a general

background of a left-hemisphere advantage for both resting and activation conditions. And again, the qEEG hemisphere asymmetry predicts the periSylvian anatomical asymmetry: a left-hemisphere advantage according to both measures. Note that the very large disparity in periSylvian volume, larger than in any of the other subjects, occurs in the context of essentially equal hemisphere volumes. The only help the anatomical-asymmetry literature can offer regarding this observation is that hemisphere-volume symmetry is fairly rare--in right-handed individuals. There is little data for "pLfL" individuals like SJ.

SJ's brainstem asymmetry once again favors the left ear, which is thus common to 3 of the 4 subjects, and does not seem related to the other measures.

CONCLUSIONS

What conclusions can we draw from these partial data on only four subjects? First, we have seen that there is a very good match between behavioral ear advantages and qEEG hemisphere asymmetries--at least in terms of the relative distribution of asymmetries for the two sound sets. And, as in the behavioral data, there are individual differences in the qEEG absolute values for each sound.

Second, there seems to be a direct relation between what we might call a qEEG "bias," and the direction of periSylvian-volume advantage: namely, that there is more qEEG beta-band power recorded from the temporal electrode overlying the larger periSylvian area. If this continues to be true in other subjects, we may eventually come to find it unsurprising--simply that the side with more neurons will generate a larger response. However, before seeing it, one might not expect it--a correlation between anatomy and rather gross physiology, apparently based on simple mass of tissue.

Finally, there does not seem to be any relation between the type of asymmetry we have measured in the brainstem response, and the asymmetries revealed in the other measures. It is possible that the PET and MEG data will provide a more meaningful bridge to the brainstem--particularly PET, which has the potential of allowing us to visualize subcortical auditory activation, in posterior thalamus and perhaps the midbrain (cf. Lauter et al 1985b. There are also other ways of measuring brainstem asymmetries (e.g., based on our repeated measures data, or using waveform derivation as described by Berlin et al 1984) that may prove to be more helpful.

In conclusion, we believe that these very preliminary data are extremely encouraging with regard to the usefulness of the strategy represented by the CNS Project. We are confident that the PET and MEG tests planned for these four subjects, and complete data sets on more subjects, will prove even more encouraging as they fill in missing details provided by techniques with better resolution and by characterizations for more representatives of each of the sidedness groups.

Certainly the within- and between-subject consistencies already seen at this early stage suggest that the CNS Project approach is not only feasible, but that it may lead us to new ways of viewing the version of the brain obtained with each of the devices. We believe also that these data give support to the prediction that by using the devices in this coordinated, complementary way, we may discover new relations between psychophysics, anatomy, and physiology, that may eventually lead to a better understanding of how the human brain accomplishes the complexities of everyday behavior.

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Fig. 1

loninvasive methods for studying brain structure & function:

natomy:
- Computerized Axial Tomography (CT)
- Magnetic Resonance Imaging (MRI)

hysiology:
- Evoked Potentials (EPs)
- quantitative Electroencephalography (qEEG)
- Magnetoencephalography (MEG)
- Positron Emission Tomography (PET)

Fig. 2

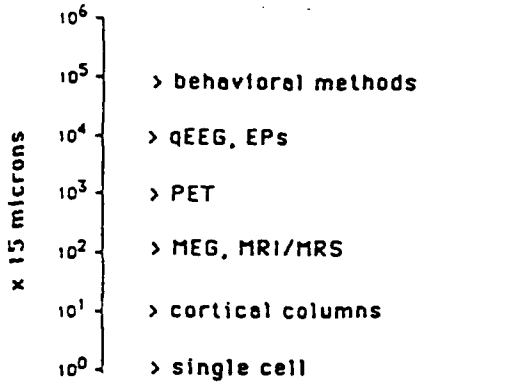


Fig. 3

HE COORDINATED NONINVASIVE STUDIES (CNS) PROJECT

- o focus on humans
- o repeated-measures design
- o behavioral "anchor"
- o anatomy
- o physiology

Fig. 4

(EA graphs: see citations for examples)

Fig. 5

Subject test schedule:

1. sidedness questionnaire and audiogram (1 hour)
2. dichotic listening (2 sound sets, synthetic stop-CV syllables and 200-ms-timed 3-tone patterns) 432 trials per ear of report per dichotic sound set (10-12 hourly sessions)
3. MRI scan (axial, coronal, sagittal series; single 2-hour session)
4. ABR series (4 weekly 1-hour sessions)
5. qEEG session (15 conditions: R- and L-ear monaural & dichotic tests with each of the two sound sets, and spaced resting conditions; single 2-3-hr session)
6. PET session (7 conditions: R- and L-ear dichotic tests with each of the two sound sets, and spaced resting conditions; single 2-3-hr session)
7. MEG session (8 conditions: R- and L-ear monaural & dichotic tests with each of the two sound sets; one run of 8 per each of two 7-detector dewar positions over each hemisphere; 2 half-day sessions)

Fig. 6

Complete CNS Project data profile for a hypothetical subject

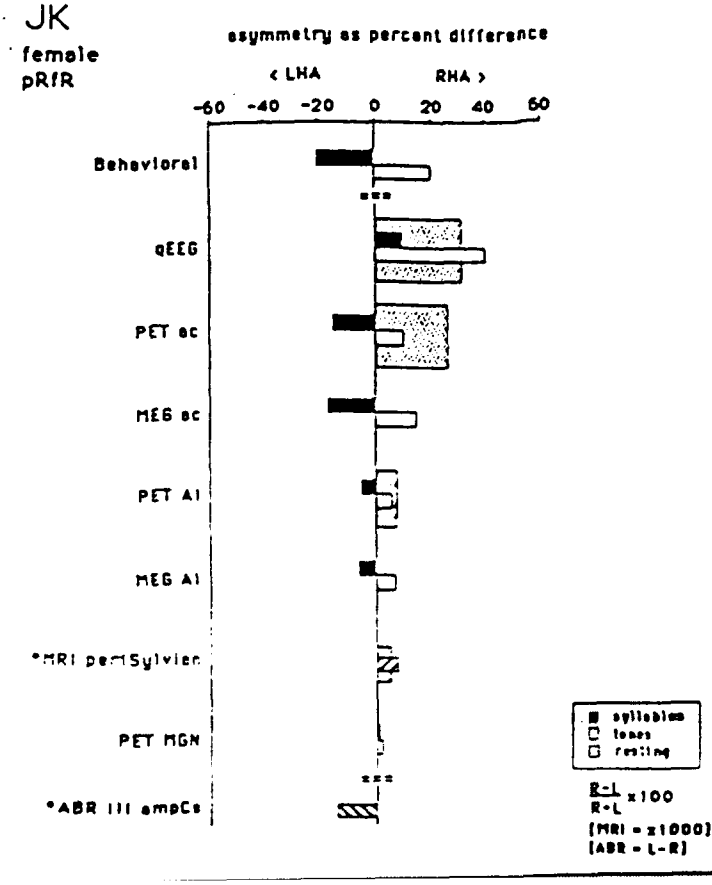


Fig. 7

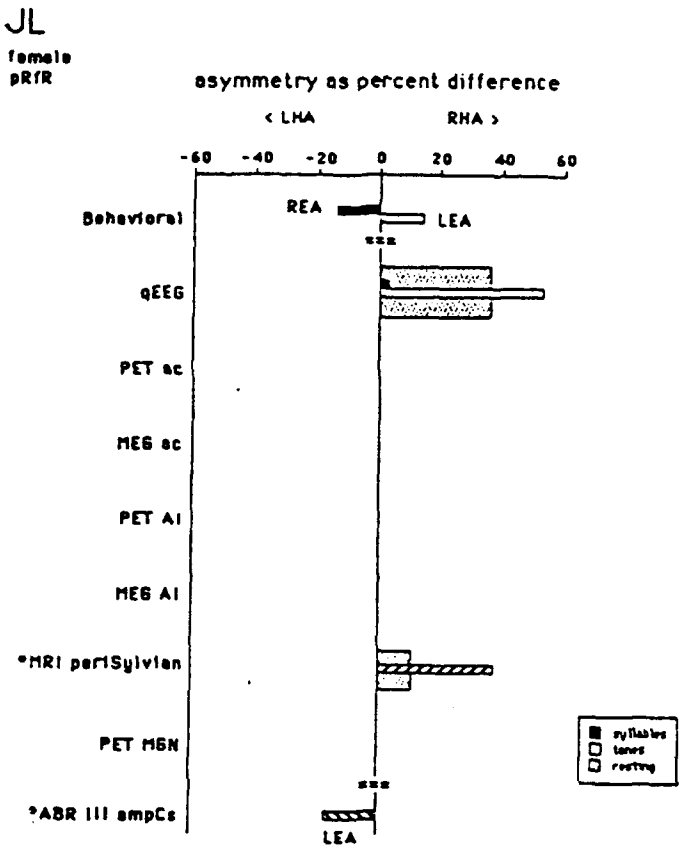


Fig. 8

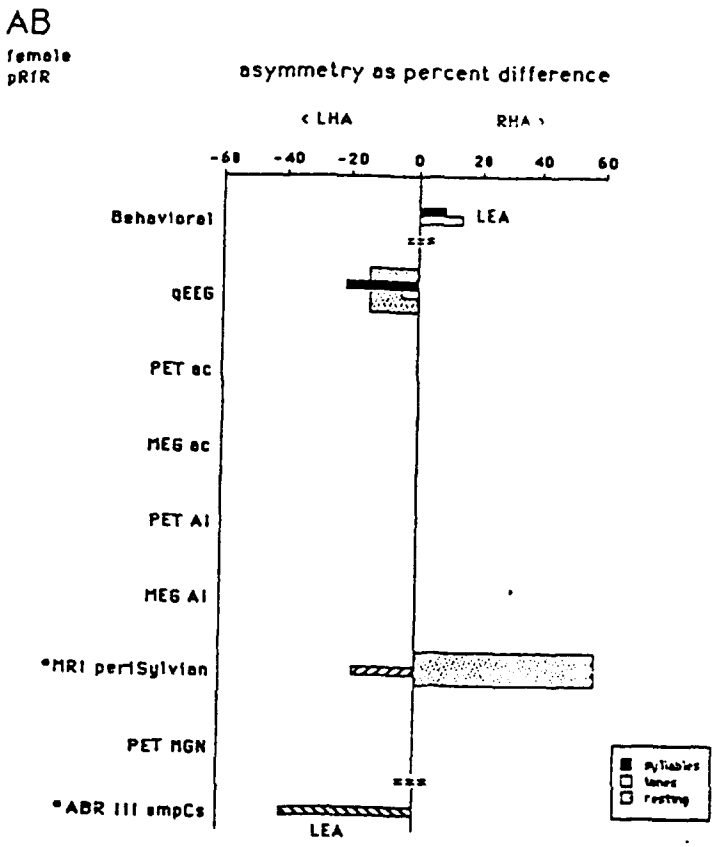


Fig. 9

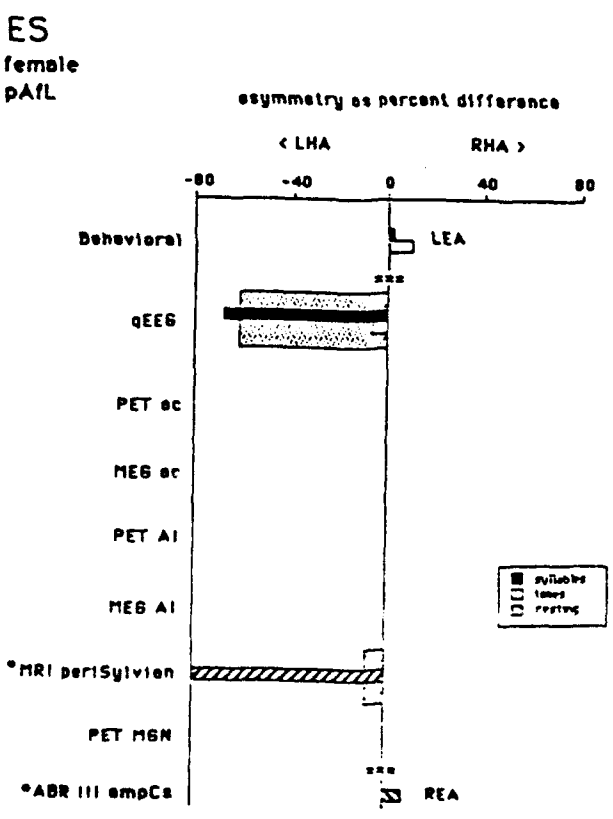
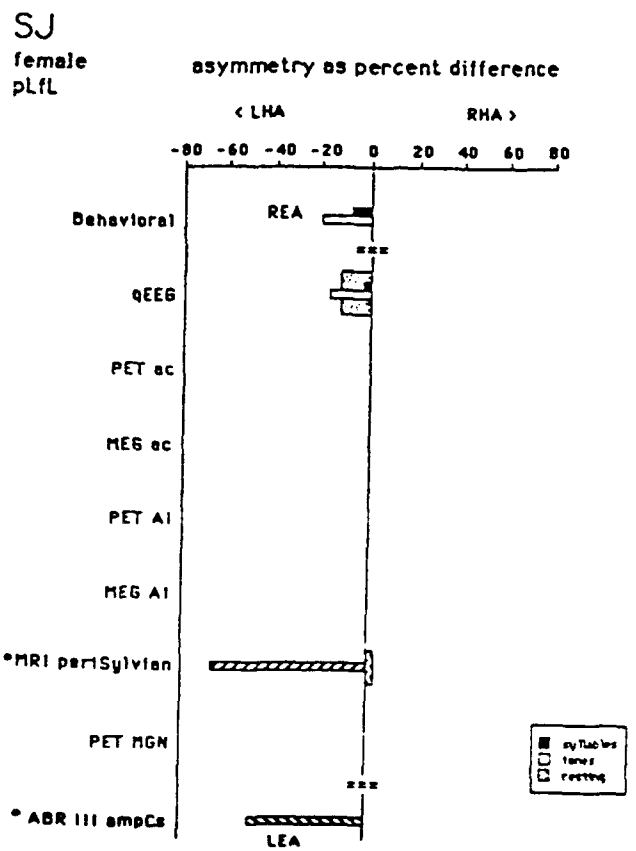


Fig. 10



COORDINATED NONINVASIVE STUDIES (CNS) PROJECT. Judith L.Lauter, Ph.D.,
Institute for Neurogenic Communication Disorders, University of Arizona, Tucson, AZ 85721.
[Presented to Society for Neuroscience meeting, October 1990, St. Louis MO]

ABSTRACT

The Project combines several noninvasive devices for studying human brain structure and function as a test battery to study aspects of behavior in the same subjects. Each individual is tested with behavioral methods, MRI, EPs, qEEG, PET, and MEG. Current focus is on asymmetries for complex sounds. First, each subject is trained on dichotic listening for two sound sets which evoke "opposite" asymmetries. Then brain anatomical asymmetries are measured using MRI, and a repeated-measures auditory EP series is done to define brainstem asymmetries. Then each subject is run on the two types of sounds while being monitored with qEEG, then PET, then MEG. Results to date show: 1) good "internal consistency" comparing behavioral, anatomical, and physiological asymmetries within subjects; 2) individual differences in the specifics of the various asymmetries; and 3) agreement across subjects in the patterns of these asymmetry "profiles." Findings suggest that this approach is not only viable, but that exploiting the complementary nature of the noninvasive techniques may reveal unsuspected relations among aspects of human neuroanatomy, neurophysiology, and behavior.

INTRODUCTION

The Coordinated Noninvasive Studies (CNS) Project is designed to exploit the complementarity of several noninvasive methods for examining human brain structure and function. This goal presents two basic challenges:

1) the formulation of an experimental question which can be addressed directly by the type of data obtainable by each method, and

2) designing a means of comparing the various dependent variables such that both qualitative as well as quantitative agreements, both within and between subjects, may be readily observed.

Our current solution to #1 is to study brain asymmetries, specifically, those related to the processing of complex sounds. Detailed quantification of such asymmetries is directly obtainable from each of the methods represented in our battery.

The solution to challenge #2 is to plot all measured values along a continuous dimension of asymmetry, which can accommodate dependent variables as seemingly disparate as percent-correct scores for syllable identification, along with the volume of cortical/subcortical areas surrounding the Sylvian fissure. By plotting values in a common space, the degree of agreement between different measures in the same subject, and between the patterns of such comparisons across individuals, may be visually as well as statistically compared.

METHODS

Subjects

Data are presented for eight subjects (seven women and one man; ages from 15 to 45), screened to have normal hearing (+/- 20 dB nHL), English as a first language, and no evidence of neurological disorder (by report).

Sidedness characteristics (e.g., "personal right-sided, familial left-handed") of each subject are reported in the results. Subjects were recruited from students, faculty, and staff at the University of Arizona, and were paid for their participation.

Test battery

1. behavioral screening: audiogram and sidedness-rating questionnaire
2. Relative Ear Advantages (RelEAs): percent-correct asymmetries for identification of synthetic stop CV syllables, and for 200-ms inter-onset-interval (IOI) three-tone patterns (cf. Lauter 1982, 1983, 1984)
3. Magnetic Resonance Imaging (MRI): whole-hemisphere and periSylvian volume asymmetries (for measures, cf. Plante et al 1989)
4. Repeated Evoked Potentials (REPs): response asymmetries in the auditory brainstem (cf. Lauter & Loomis 1986, 1988; Lauter & Karzon 1990; In Press a, b)
5. quantitative Electroencephalography (qEEG): power asymmetries in the beta bandwidth comparing activity over "auditory cortex" electrode locations T3/T4 during separate conditions testing syllables and tone patterns under monaural and dichotic directed-attention conditions (cf. Lauter 1988; In Press)
6. Magnetoencephalography (MEG): evoked-field amplitude asymmetries for same conditions tested with qEEG
7. Positron emission tomography (PET): asymmetries in magnitude of control-vs.-activation changes in regional cerebral blood flow (rCBF) for same conditions tested with qEEG and MEG (cf. Lauter et al 1985, 1988)

Procedures

After the initial screening session, each subject accepted into the Project was scheduled to begin immediately the series of dichotic-listening sessions, which took approximately two weeks to complete, and dates were arranged for the MRI scan and the REP session. Sessions for the last three tests in the battery were not scheduled until after completion of the dichotic-listening series. Thus this series acted not only to provide behavioral estimates of asymmetries related to these sounds, but also to train subjects on the tasks, to avoid the interference of novelty effects associated with task performance during later testing.

Data analysis

Results of all tests were converted into difference scores. For example, the ear-advantage identification score for each sound set is expressed as:

$$\text{Ear advantage (EA)} = \frac{\text{Right ear percent correct - Left-ear percent correct}}{\text{Right ear percent correct + Left-ear percent correct}} \times 100$$

All difference ratios except MRI were multiplied by 100, to yield asymmetries in terms of "percent-difference;" for ease of visual comparison with the other measures, the MRI difference ratios were multiplied by 1000.

RESULTS

Data for each subject tested on each of the first five tests in the battery (no MEG or PET results are as yet available) are presented as individual "asymmetry profiles" in the eight panels of Figure 1. Black bars indicate

asymmetry scores for the syllables, white bars asymmetry scores for tone patterns.

Behavioral ear advantages are plotted as though they reflect processing specialization in the contralateral hemisphere (an old idea, which serves as the "hypothesis" for each subject), and brainstem ear advantages are also plotted contralateral to the overlying hemisphere measures.

"Background" measures such as the resting qEEG asymmetry and whole-hemisphere volume asymmetry are indicated by dotted boxes. Activation results for qEEG represent asymmetries "normalized" with regard to the resting asymmetry indicated by the dotted box. Figure 2 represents a group average of these asymmetries.

Follows a summary of 9 observations:

BEHAVIORAL EAR ADVANTAGES

1. Individual differences in behavioral ear advantages: 4 show "split EAs" (EE, JL, MG, WB), 3 show LEAs for both sets (AB, CB, ES), and 1 gives REAs for both (SJ).

2. However, the pattern of relative ear advantages is the same for all individuals who are from right-handed families, i.e., black bar for the syllables is toward-the-LHA-side of the white bar for the tones; MG and SJ, a man and woman respectively, both from left-handed families, have the reversed pattern. All of these details (#s 1 and 2) are in keeping with earlier observations based on behavioral testing alone (Lauter 1982, 1983, 1984).

BEHAVIORAL vs. qEEG

3. Within-subject, there is poor agreement between behavioral vs. qEEG asymmetry pattern (whether split, both LHA, both RHA)-- in only one subject (JL) do the two methods yield the same type of pattern.

4. However, there is good within-subject agreement between the behavioral vs. qEEG patterns of relative hemisphere advantages: the six subjects whose behavioral black bar is to the left of the white bar have the identical pattern in their qEEG values; in the two subjects from left-handed families, this pattern is reversed in both behavioral and qEEG results. (cf. Lauter 1988; In Press) Thus while there is a clear relation between the two measures, it is not an uncomplicated one.

MRI ASYMMETRIES

5. Individual differences appear in the configuration of MRI asymmetries: "split" type 1 = larger whole hemisphere on the right, larger periSylvian on the left (AB, CB, SJ); "split" type 2 = v.v. (WB); both larger on the left (EE, ES, MG); and both larger on the right (JL).

MRI vs. resting qEEG

6. However, there is good agreement between the direction of periSylvian hemisphere advantage and the direction of resting-qEEG advantage, true in 7 of the 8 subjects. (The eighth is also unique in having a Chinese father.)

ABR ASYMMETRIES

7. There are individual differences in both direction and magnitude; in direction, the group is almost evenly divided-- 3 have LEA, 5 have REA.

ABR vs. MRI perilSylvian vs. resting qEEG

8. Six of the eight subjects show a good agreement between these measures, comprising a "contralateral-wiring" pattern, in which the ABR ear advantage "points to" the opposite hemisphere (MRI periSylvian volume; resting qEEG beta power). One exception is EE (with the Chinese father), whose ABR asymmetry (REA) is indeed contralateral to her periSylvian asymmetry (LHA), but whose resting qEEG shows RHA. The second exception is SJ, the woman from a left-handed family, whose ABR/MRI periSylvian/resting qEEG alignment can only be described as "ipsilateral," all favoring the left side.

INDIVIDUAL DIFFERENCES vs. GROUP AVERAGES

9. Finally, Fig. 2 presents averages of the details shown in Fig. 1. Note how the striking individual differences, as well as the size of individual measures shown in Fig. 1 are obscured in the averages of Fig. 2 (group averages show no functional differences under any condition of greater than 15%!). As we have noted before (cf. Lauter, 1982), the practice of averaging over subjects, which particularly in studies involving brain asymmetries not only seriously underestimates the size of experimental effects but also renders individual characteristics completely invisible, may prove to be a critical mistake in initial studies designed as forerunners to subsequent research, whether the projected focus is on normal individuals or representatives of clinical populations.

CONCLUSIONS

These preliminary results, for eight subjects tested with an array of six methods, suggest that the design of the CNS Project is not only viable, but that by exploiting the complementary characteristics of the different methods (analogous to combining the reports of "7 blind men looking at an elephant") we may discover unsuspected relations between behavior, anatomy, and physiology in human subjects.

It is also clear that while in some cases, values averaged over subjects may retain a shrunken, gross pattern of such relations, this practice necessarily obscures the variety of ways in which the relations are expressed in individual systems. And it is just such details which are critical for appraising measures in the next subject tested, whether another normal, or a member of a clinical group, and for generating theories regarding mechanisms.

The combination of individual differences and general patterns of organization illustrated here suggest that not until we can account for the range of individual variation will we arrive at a sophisticated understanding of the "repertoire" of ways in which human brain structure and function accomplish everyday behavior.

[Work supported by AFOSR 88-0352]

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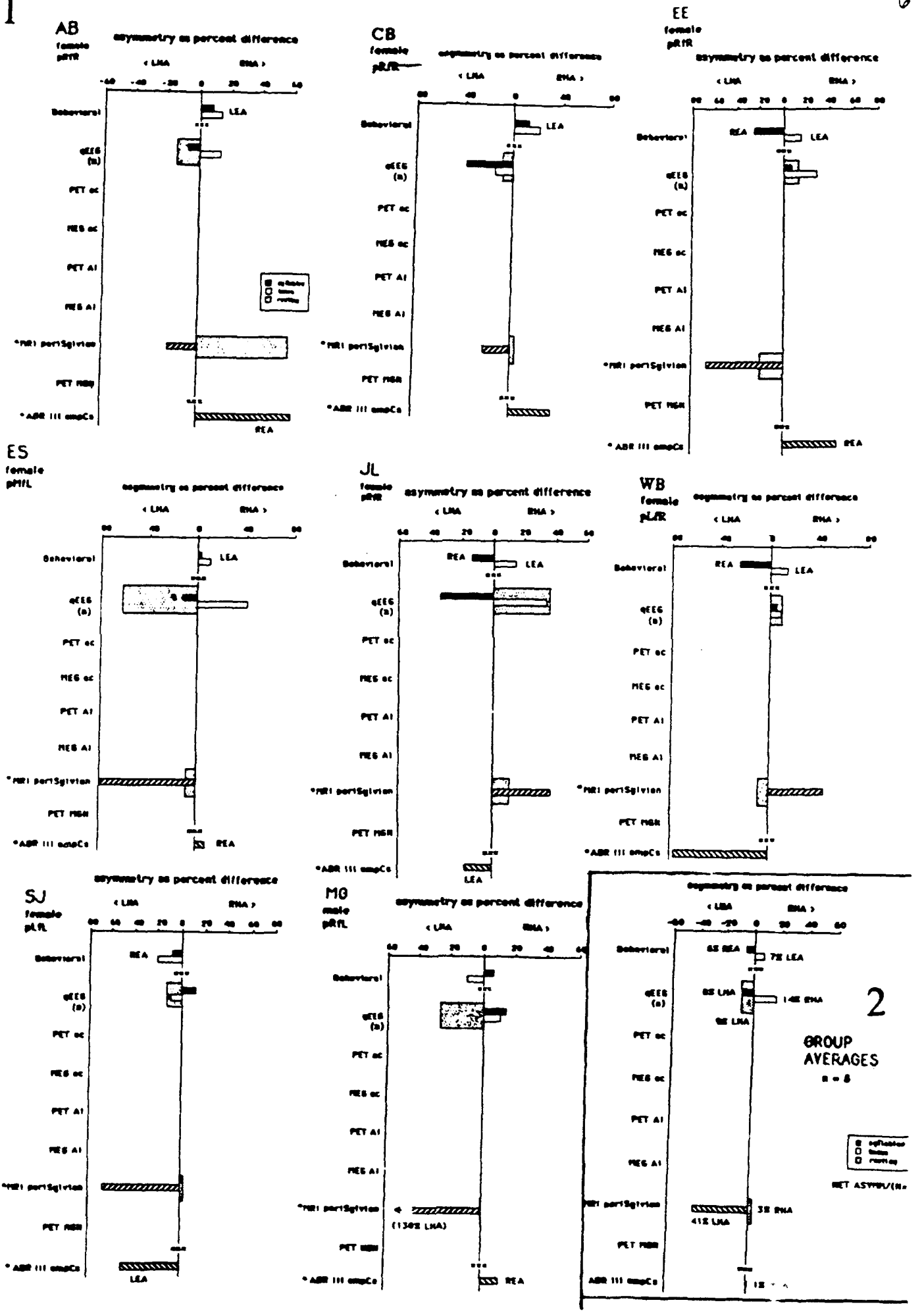
1


AB
female
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Behavioral
LEA
qEEG (b)
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REA
CB
female
pR/R
EE
female
pRfR
ES
female
pMfL
JL
female
pRfR
WB
female
pL/R
SJ
female
pLfL
MB
male
pRfL
GROUP AVERAGES
n = 8

2

Judith L. Lauter (In press) Processing asymmetries for complex sounds: Comparisons between behavioral ear advantages and electrophysiological asymmetries based on quantitative electroencephalography (qEEG). Brain & Cognition.

ABSTRACT

This experiment extends our earlier work on individual differences in ear advantages for complex sounds (Lauter 1982, 1983, 1984) to examine the results of combined behavioral and qEEG testing in the same subjects. Results include: 1) between-subject differences in absolute values together with between-subject agreements in terms of relative values, observed both for ear advantages (EAs) and hemisphere advantages (HAs); 2) within-subject agreement between behavioral (EAs) and physiological (HAs) measures of asymmetries; and 3) preliminary findings related to the interpretation of qEEG asymmetry data, such as the influence of hand movements on auditory-cortex qEEG recordings, and persistence of activation effects in which asymmetries evoked during a stimulation condition may be reflected in resting asymmetries observed during a subsequent control condition.

INTRODUCTION

Although it is generally assumed that lateralized human behavior, such as ear advantages for certain types of sounds, is an expression of underlying anatomical and physiological asymmetries, the evidence supporting this assumption has until lately been necessarily indirect. This is due to the technological and experimental limitations of previous research, and to the fact that data relevant to the question have either been derived from studies on frankly abnormal brains, or from normal brains via research procedures which introduce their own sources of variability and artefact. For example, in reviews of EEG studies of brain laterality, Gevins (Gevins & Schaffer, 1980; Gevins, 1984) has concluded that "most studies in this area have been limited by inadequate experimental designs or inappropriate analysis procedures" and, as a result, "little fundamental knowledge has been uncovered." Much the same conclusion has been voiced regarding research on human brain function using positron emission tomography (PET) to study changes in regional cerebral blood flow (rCBF) in response to different types of test conditions (Raichle 1987).

One of the characteristics both of EEG as well as rCBF studies of human brain function is the widespread dependence on group averaging. This continues to be true is in spite of the fact that many of these reports note the presence of striking individual differences, and that the medical applications toward which much of this research is aimed perforce proceed on a case-history rather than a population basis. As Gur and Reivich (1980) have noted: "The existence of [interindividual differences and intraindividual variations] in hemispheric organization may account for the fact that some studies on laterality report inconsistent, weak, or even contradictory effects. . . Furthermore, an approach that ignores these variants will be unable to account for the large variation that is known to exist in cognitive organization."

Our interests in the patterns of individual differences and agreements in ear advantages (cf. Lauter 1982, 1983, 1984), together with experience using other noninvasive physiological methods for studying the human brain (repeated evoked potentials [REPs]: Lauter & Loomis 1986, 1988; Lauter & Karzon 1990a,b, and In Press; and PET: Lauter et al 1985, 1988), have led us to

design an experiment which seeks to redress some of the problems in earlier laterality research by approaching physiological asymmetries with the same experimental-design principles used in our psychophysically-based behavioral tests. The goal of the current research was to examine the degree of within-subject correspondence between patterns of EEG asymmetry and patterns of relative ear advantages measured behaviorally for two sets of complex sounds, a set of six synthetic stop-consonant consonant-vowel (CV) syllables, and a set of six three-tone patterns.

Specifically, the experiments reported here were designed to determine whether there were physiological correlates of effects illustrated in our dichotic-listening testing: 1) between-subject differences in the absolute ear advantage (EA) shown for any one sound set; 2) between-subject agreement in terms of the pattern of relative ear advantages (RelEAs) for two or more sound sets; 3) within-subject distribution of ear advantages for different sounds which define a large dynamic range over which the dependent variable of ear advantage can vary; and 4) patterns of within-subject RelEAs which show good reliability over time. To this end, the EEG experiment was designed insofar as possible simply to add EEG monitoring to the test situation as it existed in our psychoacoustic laboratory. Hypotheses for the experiment were derived from our earlier research using both behavioral methods and other physiological testing, and are relevant to a number of issues, ranging from individual subject differences to an evolutionary hierarchy of brain asymmetries. Specific hypotheses included: 1) electrophysiological (specifically, ongoing EEG measured with quantitative EEG techniques) asymmetries can be recorded over auditory cortex during stimulation with certain types of sounds combined with directed-attention tasks; 2) when considered on an individual basis, these "hemisphere advantages" (HAs) will reflect two principles of brain organization related to processing asymmetries: a) "side of space" (in this case, right-ear *vs. left-ear input and/or attention*); *and* b) *"physical characteristics of test stimuli" (in* this case, the acoustical distinctions differentiating the syllables from the tone patterns--cf. Lauter 1983 for a discussion); and 3) the patterns of these EEG asymmetries (hemisphere advantages) will be related in systematic ways to the behavioral asymmetries (ear advantages) observed in the same subjects.

Judith L. Lauter (In press) Visions of the brain: Noninvasive brain-monitoring techniques and their applications to the study of human speech and language, In H. Winitz (Ed) Human Communication and its Disorders, Vol V.

ABSTRACT

The proclamation of the 1990s as the "Decade of the Brain" can be attributed in large part to a series of dazzling developments in brain-monitoring technology during the 1980s -- which might thus be called the "Decade of the Brain Machines." Some of these developments consisted of new applications of old principles, such as the incorporation of nuclear magnetic resonance (NMR) chemical-analysis techniques into devices for anatomical imaging, while others, such as new machine designs for imaging regional cerebral blood flow (rCBF), represented the latest step in a progression of improvements in both hardware and methodology directed to the same ends (Brown & Kneeland 1985, Ter-Pogossian 1985, Andreason 1984, Gibbons, 1990).

This chapter provides an overview of research reported during the 1980s using several of these methods to study human speech and language. The chapter is not intended as a tutorial on the methods per se (although articles and books will be cited which provide basic introductions to the principles involved in each). Rather, we will focus on the application of the methods to issues related to both normal and dysfunctional human speech and language. (A companion chapter [Lauter, In Press, a] will provide a parallel review related to the study of human hearing.)

The organization of the review is as follows: 1) major sections for each of the techniques, together with a final discussion of future developments; 2) within each of the technique sections, four separate subdivisions according to normal vs. abnormal aspects of speech vs. language; and 3) within each of these subdivisions, a brief introduction to the research that has been done and suggestions for potential studies, followed by brief illustrative discussions of two or three "focus papers" selected from the reviewed literature.

INTRODUCTION

Although we are currently approaching the threshold of the second century of neuroscience, we have embarrassingly little information about how speech and language are created and comprehended in the normal human brain, and our understanding of how those processes can be disrupted is also extremely primitive. To a large extent, this predicament results from the severe technological limitations on the study of human anatomy and physiology which have prevailed until very recently. Techniques have either been extremely invasive, or, for those sufficiently noninvasive to be used with healthy human subjects, the quality of information generated (e.g., via strip-chart electroencephalography) was so crude as to be almost useless.

Rapid progress in computer technology during the last two decades has vastly improved our ability to collect and process the otherwise overwhelming amounts of data required for sophisticated study of human behavior. Recent advances in computer design accompanied by reductions in cost have made it possible not only to study aspects of structure and function previously inaccessible (e.g., the anatomy of deep brain structures in living healthy humans), but also to increase the sophistication of experimental questions (e.g., to examine the temporal

characteristics of brain processing, and perhaps most importantly, to assess the nature and detail of individual differences).

In this review, we will consider reports of research published during the 1980s on issues related to human speech and language, based on the use of four methodologies: magnetic resonance imaging (MRI), quantitative electroencephalography (qEEG), positron emission tomography (PET), and magnetoencephalography (MEG). Methods such as computed tomography (CT), ultrasound, evoked potentials (EPs), and single-photon emission computed tomography (SPECT) will in general be considered beyond the scope of the review.

There are four basic observations to be made regarding the four techniques to be reviewed: 1) comparisons in terms of the features of body/brain; 2) characterization as "imaging" devices; 3) access to "real-time" or "snapshot" versions of structure and function; and 4) relative penetration of research and clinical practice related to human speech and language. [Preparation of this chapter was made possible by a grant from the Air Force Office of Scientific Research]

Judith L. Lauter (In Press) Imaging techniques and auditory processing, In J. Katz, N.A. Stecker, D. Henderson (Eds.), Central auditory processing: a transdisciplinary view

ABSTRACT

Although most of the nuclei of the classical auditory system are located between the periphery and association cortex, our current knowledge of human auditory function is limited almost exclusively to those two extremes. Thus the focus in professional training for audiology is on functional and dysfunctional characteristics of the outer, middle, and inner ear, with a little about the VIII nerve, and still less about cortical bases of auditory perception, since sensory components even of the posterior aphasias are poorly understood.

The function of all the portions of the system between the VIII nerve and, e.g., Brodmann areas 39 and 40, are referred to summarily as "central processing," which when disrupted results in a vague collection of problems called "retrocochlear disorders" or "central auditory disorders." It is even true that, because of design features of diagnostic tests currently in use, the acronym for the last term (CADs), should properly be read "cortical auditory disorders," since most of these tests are diagnostic only of cortical dysfunction -- cf. Lauter (1990a).

There are numerous reasons for our incomplete understanding of the auditory central nervous system (CNS), but foremost among them is the nature of the methods for studying anatomy and physiology. Until recently, most techniques have either been extremely invasive, or, for those sufficiently noninvasive to be used with healthy human subjects, the quality of information generated (e.g., via strip-chart electroencephalography) was so crude as to be almost useless.

Rapid progress in computer technology during the last two decades has vastly improved our ability to collect and process the otherwise overwhelming amounts of data required for advanced studies of human behavior. Recent advances in computer design accompanied by reductions in cost have made it possible not only to study aspects of structure and function previously inaccessible (e.g., the anatomy of deep brain structures in living healthy humans), but also to increase the sophistication of experimental questions (e.g., to examine the temporal characteristics of brain processing, and perhaps most importantly, to assess the nature and detail of individual differences).

This brief overview will focus on several methods for noninvasive brain monitoring which were applied during the 1980s to the study of the human auditory CNS. We will begin with a brief introduction to the methods, and then proceed in a "bottom-up" direction through the auditory CNS, noting on a techniques checklist which can be used to study structure and function at each level, with examples provided from the literature. (For a more complete introduction to the methods, and examples of applications to human speech and language, cf. Lauter, In Press, b; for more examples of studies in human hearing, cf. Lauter, In Preparation).

The methods to be examined are: magnetic resonance imaging (MRI), repeated evoked potentials (REPs), quantititative electroencephalography (qEEG), magnetoencephalography (MEG), and positron emission tomography (PET). Finally, a brief look toward the future will forecast the ways in which improved uses of these methods, together with the addition of new techniques, should rapidly advance our understanding of both normal and disordered central auditory processing.[Preparation of this chapter was made possible by a grant from AFOSR]

Appendix C
Unpublished report of PET study of hand flexion

Lauter, J.L., F. Tucker, K. Hubner (1990) Quantitative demonstration using positron emission tomography, of regional activation, response asymmetries, and residual effects of hand flexion in the normal human brain. In-house report, University of Tennessee Medical Center at Knoxville.

Quantitative demonstration using positron emission tomography of regional activation, response asymmetries, and residual effects of hand flexion in the normal human brain

Report of a pilot study

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Lauter, J.L., F. Tucker, K. Hubner (1990)
Quantitative demonstration using positron emission tomography of regional activation, response asymmetries, and residual effects of hand flexion in the normal human brain: Report of a pilot study

GOALS

1) demonstrate the feasibility of doing multiple-water PET sessions at this facility;
2) replicate effects documented on PETT VI at St. Louis, namely:
   a) regional activation in "hand area" of motor cortex,
   b) contralateral effects during unimanual movement,
   c) residual effects of activation conditions, i.e., regions showing high activity during performance scans continue to show moderate activity during subsequent scans, either during rest or other activation;
3) obtain new pilot data regarding the quantification of:
   a) time course of the residual effects,
   b) activity during bimanual movement, and
   c) patterns of asymmetry in regional motor cortex comparing the three activation conditions, as well the degree to which such asymmetries are reflected in the residual activation.

PROCEDURES

Subject = Fran Tucker (female; healthy adult with no history of neurological disorder; personal right-handed and familial right-handed "pRfR")
Isotope & administration = iv bolus injection of Oxygen^{15}-labelled water
Stimulation & scan timing = hand flexion begun 30 seconds preceding injection, and continuing through the 90-sec scan
Conditions tested: resting (initial, final, spaced); whole-hand flexion at 60 Hz of right hand, left hand, both hands, with the following chronology:

scan number	condition
1	resting #1
2	right-hand flexion*
3	left-hand flexion
4	resting #2
5	resting #3
6	bimanual flexion
7	resting #4
8	resting #5

[*i.e., preferred hand tested first]

RESULTS

The first goal, to demonstrate the feasibility of multiple-water sessions, was admirably achieved, with smoothly coordinated preparation and administration of the required isotope according to timing appropriate for the experiment, including cueing the subject 30 sec prior to injection, injection followed by 90-sec scan, and approximately 15 min between the end of one scan and cueing for the next. Samples produced were all calibrated at 70 mC, with the exception of the first sample (scan omitted for analysis) and the eighth (60 mC). Because of the sample failure in scan #1, a total of 9 scans were conducted in a session that required approximately 2.5 hrs, an optimal and excellent test time even in laboratories which have more practice in doing multiple-water sessions.

As for the other goals of the study, a discussion of the analysis strategies utilized and results observed will illustrate that all goals, both those involving replication of previous results as well as those regarding new observations, were realized.

Selection of regions of interest (ROIs). In order to analyze the result of each scan in the study, the 15-slice images created by the ECAT were reproduced onto film for viewing, one set of 15 per each of 8 scans. Second, the Analyze software was used to create an interpolated 42-image series for each scan, to be viewed and processed for regional quantitative analysis on the Sun workstation. Preliminary visual examination of the original 15-slice series suggested that there were two restricted ROIs occurring in the upper slices, specifically in slices 2 and 3 of this series, in which the degree of activity seemed to change with task manipulation. Subsequent examination of the 42-slice interpolated series viewed on the Sun workstation indicated these ROIs could in fact be identified as undergoing different degrees of change throughout the session, and such changes were restricted to the top 5 slices, #38 through #42.

Figure 1 represents the two ROIs thus defined, as they appear on interpolated slice #38, each described with a circular cursor of radius=3 enclosing 32 pixels. The left-hemisphere cursor is centered at (76,76), and the right-hemisphere cursor at (48,73). In order to establish that these two ROIs were the primary areas in the brain affected by the task manipulation, and that analysis should focus on changes in these regions only in slices #38-42, a quantitative analysis series for all 42 interpolated slices was done for the LH region, comprising a "core" extending through the targeted LH ROI identified in slices 38-42, caudally through the entire 42-slice series.

Figure 2 graphically displays the results of this analysis, plotting activity units determined by the Analyze program (possible range = 1 - 250) on the ordinate, as a function of slice, shown on the abscissa. The panel on the left shows results for analysis of the resting scans only, with six lines, each representing the cross-sectional "profile of activity" in the identified region during one of the six resting scans. Consideration of the original 15-slice series suggests that the regions showing consistently very high activity throughout the session (on slices #18-21, 24-26) may represent mesial temporal/inferior frontal cortex (slices #18-21) and superior-temporal-plane cortex (slices #24-26). Both of these regions have been shown to

be activated by auditory input (Lauter et al 1985, 1988), and thus we might reasonably interpret the observed activity levels as indicating chronic acoustic stimulation throughout the session, particularly in view of the fact that no ear protection was employed.

In these rostro-caudal cross-sectional activity profiles, there are few changes throughout the brain from resting scan to scan. In contrast, the panel on the right duplicates the function from the left panel for the initial resting scan (indicated by the single line without point symbols), and combines it with the plots of activity for all 42 slices during the three activation scans. Note that the activation functions are essentially identical with the resting function for all slices-- except for those slices at the very top of the series, #38-42. For these portions of the functions, note that for this LH ROI, there is no change vs. the control function during the left-hand condition, but that during both conditions in which the right hand is involved, right-hand and bimanual flexion, there are clear differences compared with the control function. On this basis, it was concluded that further analysis of effects during the session could be meaningfully restricted to consideration of slices 38-42.

Activity changes in 5 slices. The five panels of Fig. 3, one for each of these five slices, presents the same measure of activity (from the Analyze 250-value range) from Fig. 2 (plotted on the ordinate) as a function of scan (plotted on the abscissa). The gross patterns of activation appear quite similar in all five slices: the LH ROI is most active during right-hand and bimanual flexion, the RH ROI is most active during left-hand and bimanual flexion, and both ROIs show decreased activity during the resting scans. However, there are small differences from slice to slice, a fact which reminds us that these interpolated slices are artificial subdivisions of the original data set, "artificial" in that they are software-created images formed from the array of data collected as the original 15 hardware-based slices (i.e., where slice configuration is determined by the physical characteristics of the ECAT detector rings). Thus attention was given to analyzing the results for each of these 5 "software slices" in order to see which might most accurately represent the "hand area" of motor cortex, the intended target of the study.

Patterns of asymmetry in activation scans. The central difference posited in this study to occur between activation of the two ROIs had to do with the degree of asymmetry evoked during each scan. Thus a value of hemisphere asymmetry was calculated comparing the activity in the RH vs. the LH ROI under each scan condition. The value of the asymmetry was computed as the percent difference between the two ROIs: [RH - LH / RH + LH] x 100. Eight such asymmetries were calculated (one for each of the 8 scan conditions) for each of the top five slices (#38-42), plus a slice somewhat below this set (#35), chosen to be a "non-motor-cortex" control region similar in level of resting activity to our five candidate slices yet which did not seem to be affected by the task manipulations. Figure 4 presents the percent-difference asymmetries observed during the activation scans in the single control and five target slices (see legend for symbols), with degree of asymmetry (a continuous dimension divided into left-hemisphere advantages LHA vs. right-hemisphere advantages RHA) on the abscissa, plotted as a function of scan (ordinate), in the form of "asymmetry profiles" for the six slices over time.

If the ROIs in a particular slice showed no change in relative asymmetry over time, the asymmetry profile for that slice would appear as a straight line on this graph. As expected, slice #35 shows the least effect of the manipulations--its profile does not deviate much from a straight line--and slice #38 shows the next smallest effect. However, the asymmetries comparing the two ROIs in each of slices 39-42 seem equally affected by the changes in activation conditions. Thus this comparison suggests that: 1) slice #35 may be most distant from motor cortex, 2) slice #38 may be somewhat inferior as well, since it does not show quite the extreme changes observed in the five slices superior to it, and 3) based on the activation scans, the top four slices seem to show equally dramatic changes with test condition.

Of course, it is possible that these four "software slices" (#39-42) all represent data originating in the hand area of motor cortex. However, if we assume that the implied thickness of each such slice is between 2 and 5 mm, this is clearly not possible. Experience with patterns of brain asymmetries observed with qEEG (Lauter 1988a) suggests that a more sensitive index of localized brain activity might be the pattern of asymmetry observed not during activation conditions, as in Fig. 4, but during resting conditions collected subsequent to activation conditions. We have observed that resting asymmetries not only provide information regarding an individual's characteristic "resting bias" in some brain region (i.e., favoring the left vs. the right side), but can also reflect residual effects of preceding activation.

Residual-effect asymmetries during resting scans. Our hypothesis in the current context is that those "software slices" which show residual effects most similar to preceding activation provide the closest approximations to the location of targeted cortex, on the assumption that brain regions actually stimulated by a task will show the longest after-effects. Figure 5 presents asymmetry profiles comparing our two ROIs, for resting scans only. Symbols for the different slices are the same as used in Fig. 4. If none of the slices showed residual effects, all of the profiles would consist of straight lines, with no changes in asymmetry from initial through all resting scans. Note in fact that our "non-motor-cortex control" slice, #35, shows very little residual effect of the activation scans, demonstrating a fairly linear drift from an initial resting asymmetry of 5% LHA toward an enhanced LHA of 12% by the final resting scan.

As a side note, this departure from a "straight-line" resting-asymmetry profile, comprising a "leftward drift" of resting asymmetry over the course of a PET session in normal subjects, has been observed previously (e.g., Perlmutter et al 1987, and Lauter & Plante 1989). It has been suggested that this phenomenon is the result of a change in anxiety level from the beginning of a session (higher anxiety) to the end of the session (lower anxiety), and that the change in subject reaction is expressed in the PET images by a change in relative activity in the two hemispheres, specifically with the right hemisphere showing relatively more activation early in the session and relatively less later on. The "relative" part of the statement is essential, predicting that, depending on the individual subject, this leftward drift may involve either a diminution in an initial RHA, an actual shift from RHA to LHA, or an enhancement of

an initial LHA, as in this case.

Resting-asymmetry profiles for the other five slices shown in Fig. 5 reveal much more distinction among the five than was true in the activation profiles of Fig. 4--and note that all of the details shown here are in terms of residual effects only. The resting-asymmetry profile for slice #38 departs from a straight line only twice, first during the resting condition immediately following the pair of unimanual conditions--and the departure is in the same direction as the asymmetry for the preceding activation (left-hand flexion: cf. asymmetry value for slice #38 during this condition shown in Fig. 5)--and the second time seeming to participate in the leftward drift of slice #35. The case is similar for slice #41, without the leftward drift at the end. The profile for slice #42 is exactly a straight line, revealing no residual effects at all. Thus we might conclude that of these three, slice #38 is inferior to and furthest from motor cortex, behaving at least in part much like underlying brain regions (slice #35); slice 42 is next furthest away, in a superior direction, without the leftward drift of lower regions but also showing no residual effects of activation; and slice 41 is closest of the three, perhaps just superior, with a small residual effect following left-hand movement, but no leftward-drift effects.

This leaves the "software slices" #39 and 40, which show clear residual effects following both the unimanual and bimanual conditions. There is no evidence here to help us select one of the slices as the best candidate for "motor cortex:" slice #39 is more dramatically affected than is slice #40 following unimanual flexion, but the reverse is true following bimanual flexion. At this point, we may be interpretatively slicing the data too thin, and perhaps should tentatively conclude that the combination of activity changes observed in software slices #39 and 40 represents the best approximation to localized activation in the hand area of motor cortex in these data.

Summed "software slices." Thus assuming that the most accurate representation in the "software-slice" series of motor cortex stimulated in this study are slices 39 and 40, we may combine their data, summing activity counts in the two ROIs in these two slices, and then re-calculate percent-difference asymmetries in order to observe the changes across the chronology of the session. Figure 6 presents the results of these calculations, providing a summary of the major brain-asymmetry effects observed in this study:

1) clear contralateral dominance during unimanual flexion (large left-hemisphere advantage during right-hand movement, similarly large right-hemisphere advantage during left-hand movement--in agreement with previous results, cf. Raichle 1987 for a review);

2) only very slight dominance during bimanual flexion (small RHA for this subject);

3) asymmetries evoked during activation scans persist in reduced form during subsequent resting control scans (e.g., C2 still shows a small RHA, C4 reflects the RHA observed during the preceding bimanual condition), and these residual effects seem to be resolved within 30 min following the relevant activation (C3 and C5 asymmetries are back at zero, matching C1).

DISCUSSION

While data from additional subjects are needed in order to test statistically the generality of the current findings, these effects are dramatic enough, and in the predicted directions, to justify a preliminary conclusion that it is possible to use PET to demonstrate "side of space" asymmetries based on simple hand flexion. Also, we may predict that details of these asymmetries, such as contralateral effects, reduced asymmetry during bimanual flexion, and the time course of residual asymmetries observed in control scans subsequent to activation scans, may be studied in useful ways both qualitatively and quantitatively.

Bi-hemisphere coordination. Although this subject responded entirely as would be predicted given her characterization as a personally right-sided, familially right-sided individual, it is possible that individuals from other sidedness groups might show different patterns, e.g., asymmetries weighted toward one hemisphere or the other during unimanual conditions, or more clear influences of one hand or the other during bimanual flexion. With data from only one subject, we cannot tell whether the small difference in the unimanual-condition asymmetries (from Fig. 6, 12.4% LHA during right-hand movement vs. 10.6% RHA during left-hand movement) and the very small asymmetry during bimanual flexion (0.34 % RHA), echoed in the somewhat enhanced asymmetry (2.2% RHA) during the subsequent control scan, are important reflections of individual characteristics. It is possible that such differences will be enhanced in other subjects, e.g., reflecting the influence of "learned dominance" (i.e., the preferred hand will always evoke a larger asymmetry than the non-preferred hand--as in this subject's data where right-hand flexion evoked a larger asymmetry than left-hand flexion), and/or the importance of "difficulty" during two-hand coordination (i.e., being forced to include the nonpreferred hand in bimanual flexion results in an asymmetry favoring the side opposite that hand--as in this subject's small RHAs during the bimanual and the subsequent resting scan).

Comparisons of PET and qEEG. Certainly our earlier observations based both on PET data and qEEG results (Lauter 1988b) of the time course of physiological residual effects are borne out in these data, supporting our original estimate of a minimum of 20 and a maximum of approximately 30 minutes required for the regional effects of activations such as hand flexion and complex-sound identification to be resolved. Observation of the behavior of resting asymmetries such as those illustrated in Fig. 6 certainly justifies further research on this question, using both PET and qEEG. The patterns of Fig. 6 suggest the most efficient experimental design might utilize a single pair of "equal and opposite" activations to demonstrate the effect, with at least two control scans separating the activations; thus, a session consisting of an initial control, preferred-hand flexion, two controls, non-preferred-hand flexion, two controls would provide two opportunities to observe the time course of the resolution of persisting residual effects within the same subject. Certainly it would be of interest to compare estimates of the residual-effects time course in the same subject measured with PET and with qEEG. The advantage of qEEG for this type of study is that one can

document the time course of residual-effect resolution with finer temporal sampling, since meaningful measures of qEEG asymmetries can be made in successive 2-min intervals.

A preliminary comparison of this type is indicated in Fig. 7, where the data for the current subject (FT) are displayed in a slightly different way, comparing the asymmetry of the two ROIs during first control (C1), left-hand movement (circled "L"), and second control (C2) scans [data from Fig. 6], with similar asymmetries for four other subjects, but based on quantitative EEG measurements over motor cortex (electrode locations F3/4 or F7/8) during testing under identical conditions. Note that the qEEG data show the same effect as FT's PET results, i.e., the resting asymmetry observed during the second control scan is shifted away from that of the original control in the direction of the asymmetry evoked by the immediately preceding activation condition, whether for right-, left-, or both-hand flexion. Subject WB's data even provide an instance of resting-asymmety "overshoot" following activation, similar to the PET results for subject FT (Fig. 6), in which the resting asymmetry for "C4" goes even further and in the same direction as the asymmetry evoked by the preceding bimanual condition. Note also that the magnitude of the effect illustrated in Fig. 7 is quite similar for qEEG vs. PET data in spite of the physical and chemical differences underlying the two brain-monitoring methods, which suggests that both methods provide comparable versions of the same phenomenon. The Coordinated Noninvasive Studies (CNS) Project (Lauter 1989) is concerned with direct comparisons such as these in the same subjects, and is designed to examine the degree to which the version of such patterns of brain response studied in the same subjects are exactly coincident from technique to technique.

Methodological issues. With regard to more methodological concerns, future testing is also needed to determine whether the analysis strategies developed here will continue to prove useful in examining the data for other subjects tested on hand flexion, as well as for other activation conditions, such as auditory and visual stimulation. The strategies include: 1) selection of ROIs based on examination of both the "hardware-slice" series and the "software-slice" series of images; 2) validation of approximate anatomical localization of activated regions via cross-sectional rostro-caudal "core" analysis through the selected ROIs, in order to triangulate by means of hypothesized profiles of resting activity levels in other brain areas; 3) selection of those "software slices" which best represent the targeted brain area, based on the assumption that the pattern of residual activity observed during resting scans is a more sensitive index of regional brain activation than are patterns of activity during stimulation scans.

Conclusion. In summary, all stated goals of this single-subject pilot study have been realized. It is clear that the test facility can accommodate experiments requiring multiple sequential O-15 injections, and that the resolution of the imaging hardware and software renders localized activation and residual effects both visible and quantifiable. The potential promised by such findings for basic research on human neurophysiology is tremendous, and may be turned to a myriad questions regarding brain asymmetries and coordination, as well as considerations of brain mechanisms involved in activation, such as the puzzle of the persisting

residual effects described here. Recommended studies for the immediate future are those which are designed to take advantage of the potential of this system to study basic aspects of brain response in normal human subjects, including complementary designs in which results on MRI, qEEG, and PET are compared in the same individuals, in order that we may better understand the degree to which the physics and chemistry of PET affect the picture it provides of patterns of human brain function.

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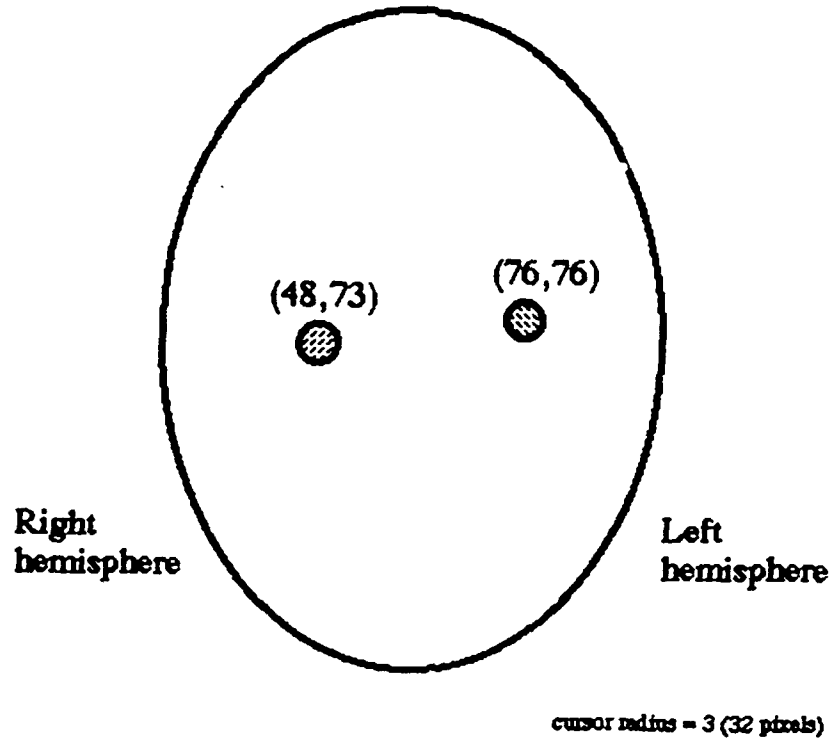


Figure 1. Regions of interest (ROIs) selected for analyzing the effects of hand movement in subject FT. These ROIs were chosen based on visual inspection of the "subtraction" images representing change from control to hand-flexion activation, generated by the Analyze software.

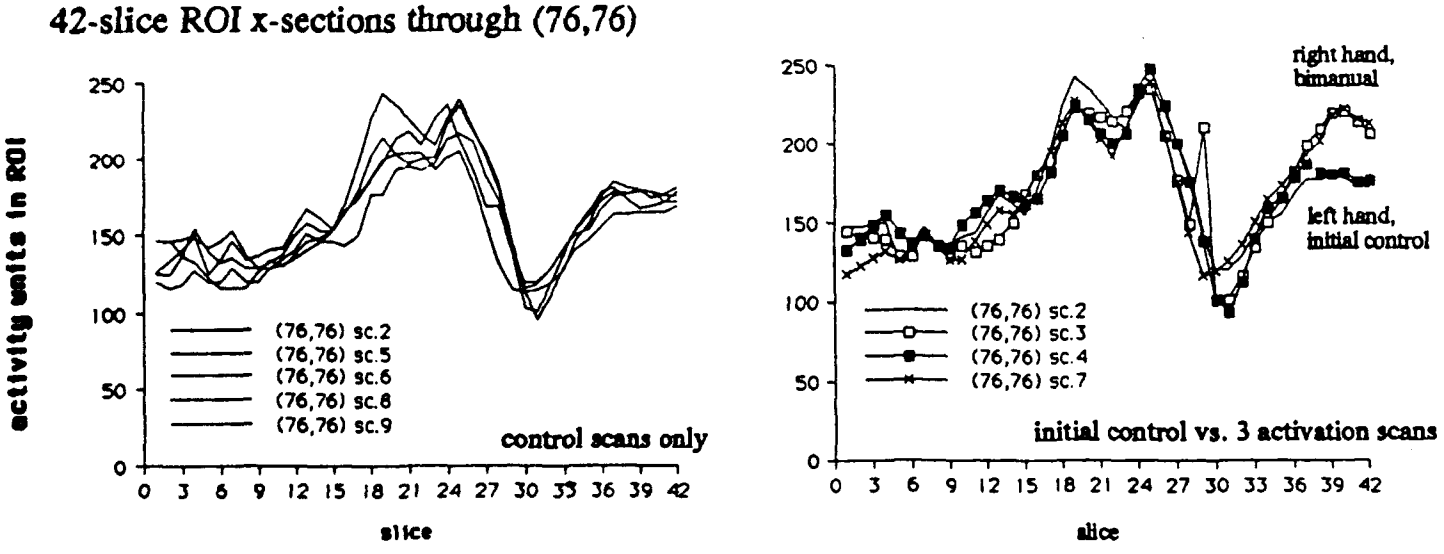
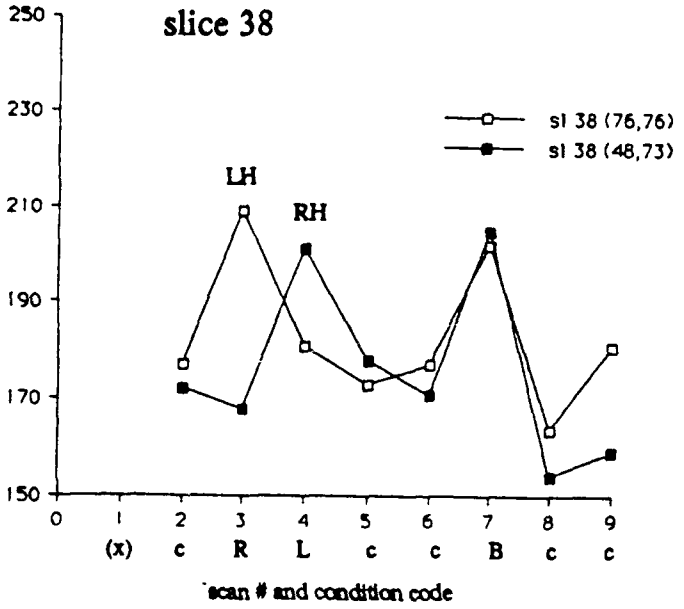


Figure 2. Cross sections through the vertical extent of the brain based on the left-hemisphere ROI of Fig. 1. Left panel: profile of activity in this rostro-caudal "core" during each of the six control scans in the session: note the minimal change across control scans, together with the dramatic differences in the level of activity at different locations along this vertical dimension. Consideration of the original "hardware slices" suggests that the two regions of very high activity (slices #18-21, #24-26) may represent mesial temporal/inferior frontal cortex, and primary auditory cortex--both susceptible to auditory stimulation, which was available throughout the session since no ear plugs were used. *Right panel:* profile of activity through this "core" for the three activation scans and the initial control scan from the left panel. Note that only slices #38 and above show a distinction based on experimental manipulation, with this left-hemisphere ROI showing more activity during right-hand and bimanual movement and less (comparable to control) during left-hand movement.



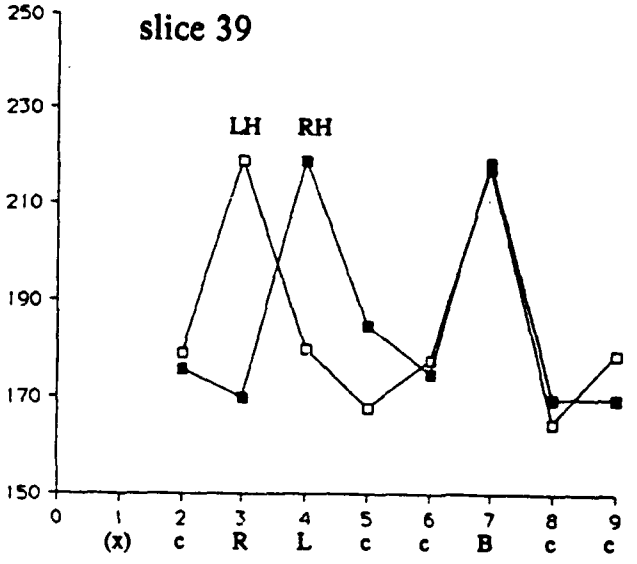
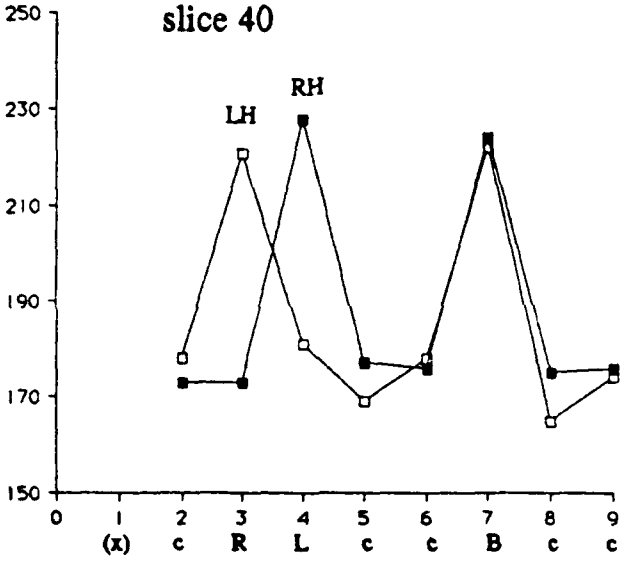
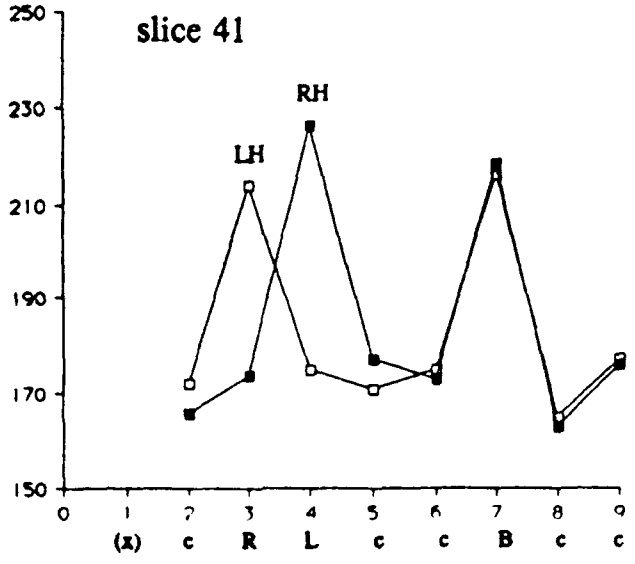
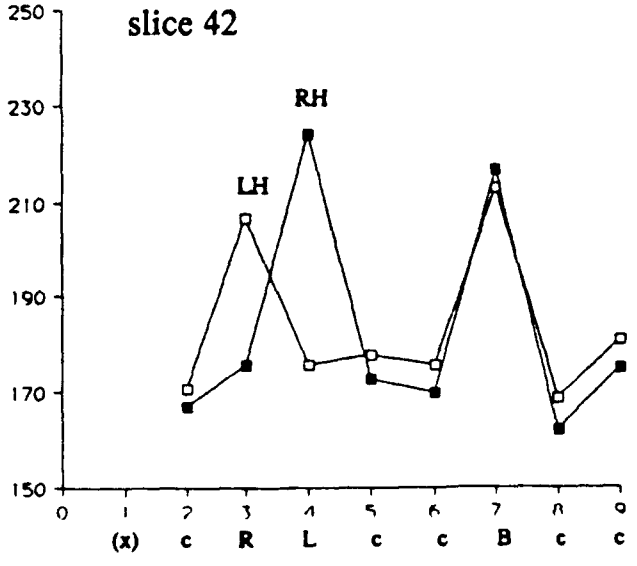


Figure 3. Activity calculated in each of the two ROIs (parameter) measured in 5 slices of the series from Fig. 2 (one panel per slice), and plotted as a function of scan for the 8 test scans of the session: an initial resting (control) condition, right-hand flexion, left-hand flexion, two controls, bimanual flexion, two final controls. Note the differences from slice to slice, prompting an examination (see text and following figures) of which slice or slices represents the most accurate version of "real" brain activity.







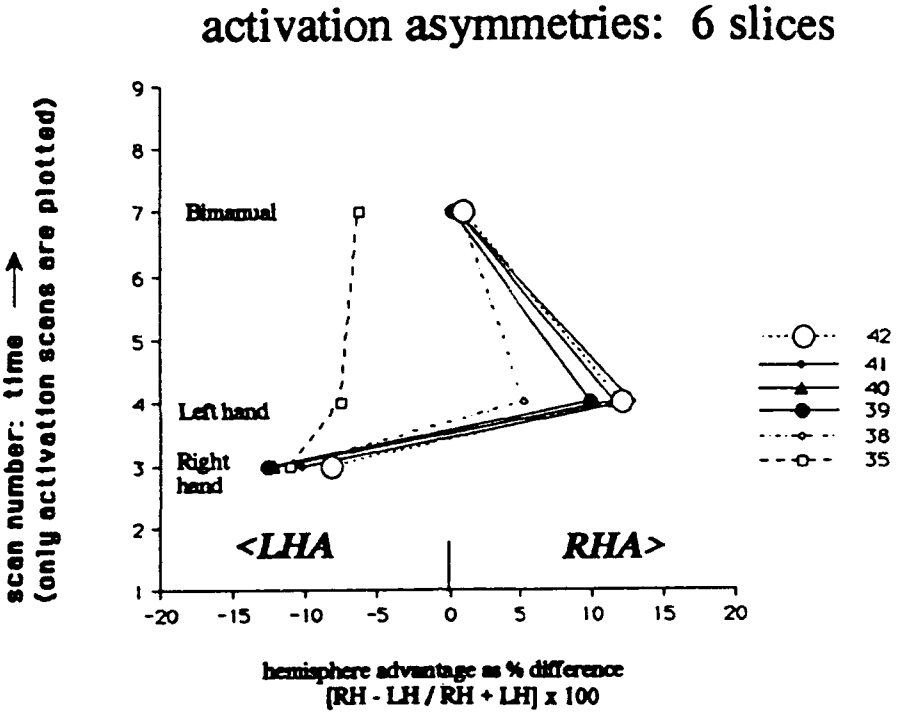


Figure 4. Asymmetries (abscissa) comparing activity in the two ROIs, for each of the five slices from Fig. 3 (parameter) together with a fifth, inferior and supposedly non-motor-cortex slice, for each of the 3 activation scans (ordinate). The inferior slice #35 does in fact show few effects of the stimulations, #38 shows somewhat more change, and the top four slices seem equivalent.

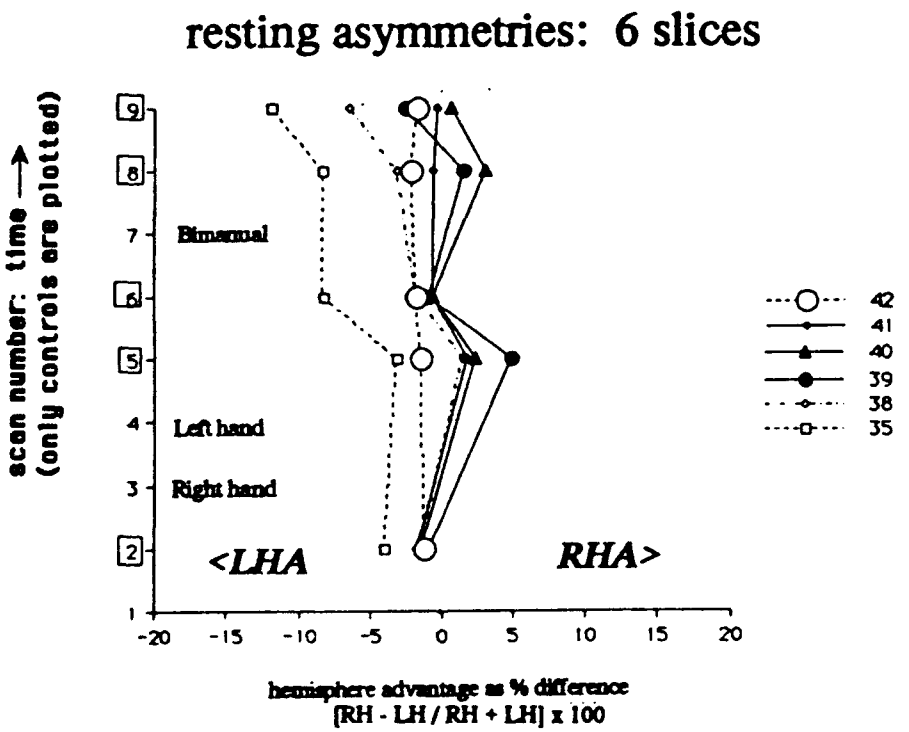


Figure 5. Asymmetries (abscissa) comparing activity in the two ROIs, for each of the six slices from Fig. 4 (parameter), for each of the six control scans. The "residual effects" illustrated here indicate that slices #39 and 40 show the most dramatic persisting effects of activation, and thus may be concluded to offer the closest approximation in these data to the level of the hand area of motor cortex.

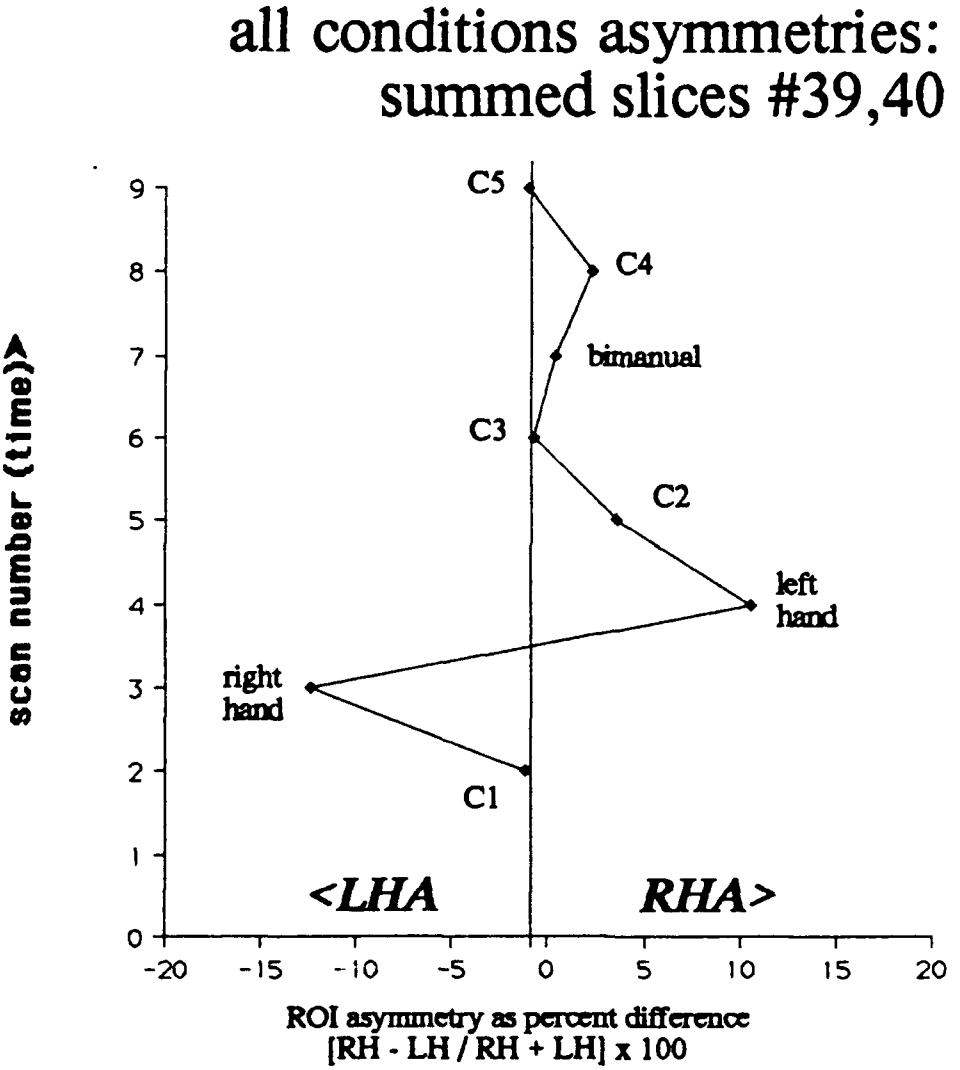


Figure 6. Summary of the results from this experiment, based on the asymmetry between the two ROIs measured on slices #39 and 40 only, for all 8 test scans. Note the clear and large contralateral effect during the two unimanual test conditions, the residual effect in control scan C2, the very small asymmetry during bimanual flexion, the residual "overshoot" in control C4, and the return to initial-control baseline in C5.

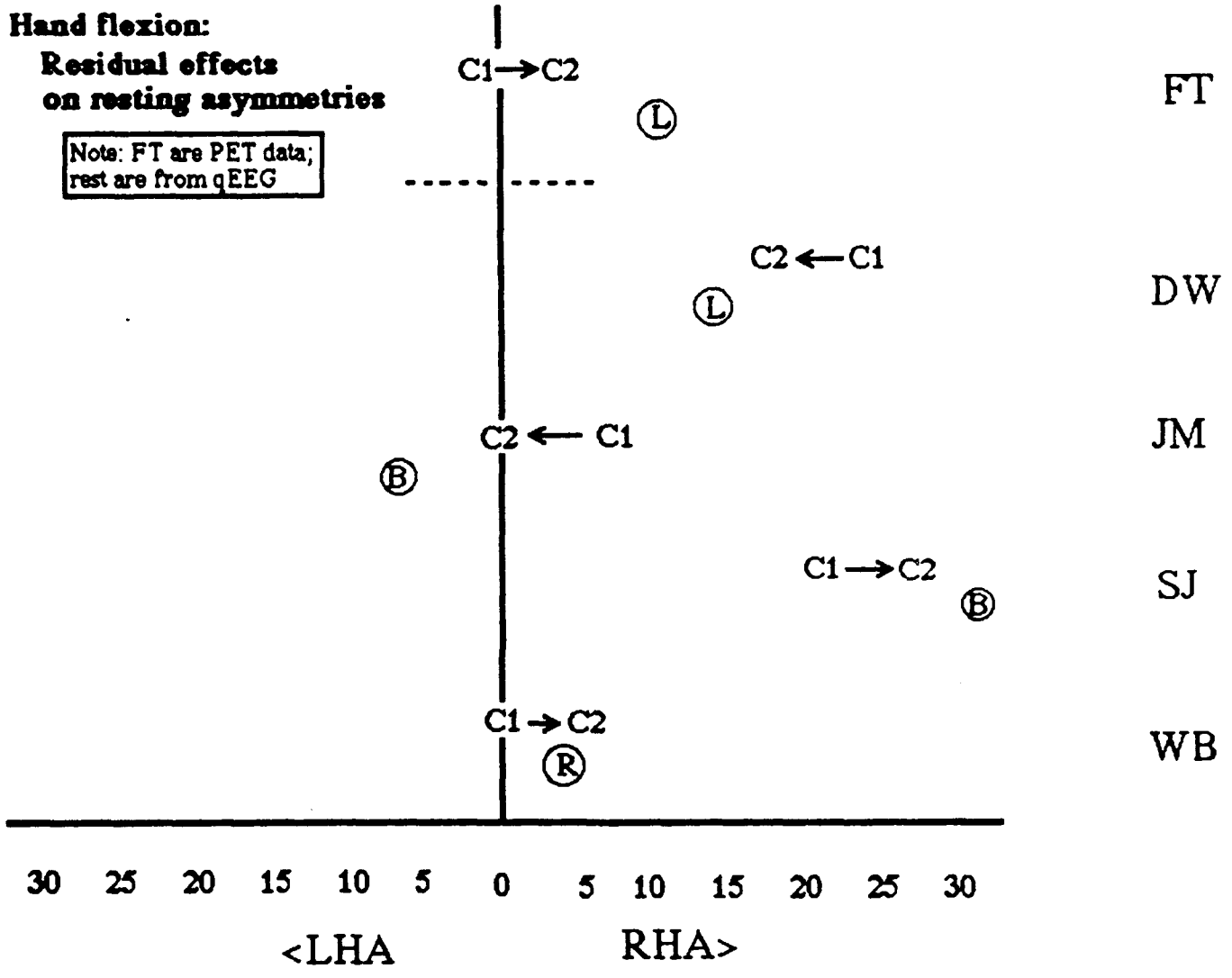


Figure 7. Comparison of the degree of "residual effects" in terms of resting asymmetries observed in control scans following hand-movement activation, either with PET (subject FT) or qEEG (other four subjects. A proposed follow-up to the current PET study is to test subject FT with qEEG to determine whether these two brain-monitoring methods provide comparable measures of this type of residual effect in the same individual.

Appendix D.
Related activities I: Repeated Evoked Potentials (REPs)

1. Summaries of unpublished reports:

Lauter J (1990) " 'The smoker's needle:' Sign of a pre-existing neurological condition in addicted individuals?"

Lauter J (1991) "qEEG correlates of the 'smoker's needle:' Observations in an addicted smoker with a history of hyperactivity treated successfully with Ritalin"

2. Texts of meeting presentations:

Lauter, J.L. and R.F. Oyler (1989) "Comparisons of between- and within-subject variability in repeated-measures auditory brainstem responses (ABRs) in 10-12-year-old children, presented to Acoustical Society of America, St. Louis MO. Abstract: J Acoust Soc Amer 86: S45.

Lauter, J.L. and J.M. Lord-Maes (1990) "Repeated-measures auditory brainstem responses (ABRs): comparisons of stability profiles based on different time schedules," presented to Acoustical Society of America, State College PA. Abstract: J Acoust Soc Amer 87: S64.

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Lauter, J.L. (1991) "Central auditory dysfunction: qEEG correlates of individual differences in ear advantages and REP/ABR results," presented to Acoustical Society of America, Houston TX. Abstract: J Acoust Soc Amer 90: 2292.

UNPUBLISHED REPORT #1

Lauter JL (1990) " 'The smoker's needle:' Sign of a pre-existing neurological condition in addicted individuals?"

The protocol now referred to as "Repeated Evoked Potentials" or "REPs" has evolved out of our work with repeated-measures evoked potentials based on experiments begun as early as 1983. As the texts of meeting presentations from 1989-1991 listed above indicate, continuing developments in the REPs protocol have been in the direction of clinical applications, outside the domain of our AFOSR-funded research on normal subjects. Support for REPs work has depended on collaborations with several institutions, and has involved sharing of both personnel and equipment.

One clinical application is related to individuals practicing substance abuse. Recent theory regarding these individuals includes the concept of "self medication," according to which at least some addicted individuals are posited to have a neurological condition pre-dating substance abuse (perhaps genetic, or induced by maternal substance abuse during pregnancy), a condition which they come to "treat" by self-administering one or more substances. A given individual may use a variety of substances, or may select a "substance of choice" which best resolves the adverse effects of the particular neurological abnormality.

During the summer of 1990, the opportunity arose to conduct a controlled within-subject design with a woman and her husband, where the woman reported herself to be addicted to cigarettes (i.e., found it exceedingly difficult to quit) while the husband reportedly could stop-and-start smoking at will with no perceived ill effects. The two individuals were recruited for a three-session "on-off-on" REPs experiment: session one to be conducted during a period when both were smoking at their usual rate of >1 pack per day, session two scheduled to occur at least 1 week following session one and at least 3 days after both stopped smoking "cold turkey," and session three scheduled conditionally according to their subsequent behavior: 1 month after session two if they continued to abstain, or at least 1 week after session two if they returned to smoking.

Each session consisted of the REPs protocol used in the experiment on multiple sclerosis reported in 1990 (for details, see meeting presentation text below), with collection of 4 left-ear, 4 right-ear, and 8 binaural waveforms. Results were analyzed by: 1) selecting the first five vertex-positive peaks on all waveforms; 2) calculating the mean latency and mean amplitude, and well as latency stability and amplitude stability for all peaks under all ear conditions (stability defined as Coefficient of stability [Cs] = mean / standard deviation); 3) comparing these data

for each subject tested in each session against a normal database; and 4) calculating the distribution of resulting "REP scores" for each ear condition in each individual tested in each session.

While "REP score profiles" derived from the calculations of step #4 above had proved to be most useful in our study on MS (see the meeting presentation), the most striking effects in this experiment on smoking were to be found in the comparisons with normals made in step #3, specifically, in comparisons of latency stability observed during binaural stimulation conditions. Results for the (addicted) woman (HR) are presented graphically in Fig. R1. The large filled circles represent the individual data, compared against a range template describing the normal database (mean = fine line; +/- 1 standard deviation = dotted lines; +/- 3 standard deviations = heavy lines). As these figures show, this subject's data were within normal limits ONLY DURING THE SESSIONS WHEN SHE WAS SMOKING; during the abstaining session, her data showed a clear hyperstability of latency at ABR peaks III and IV.

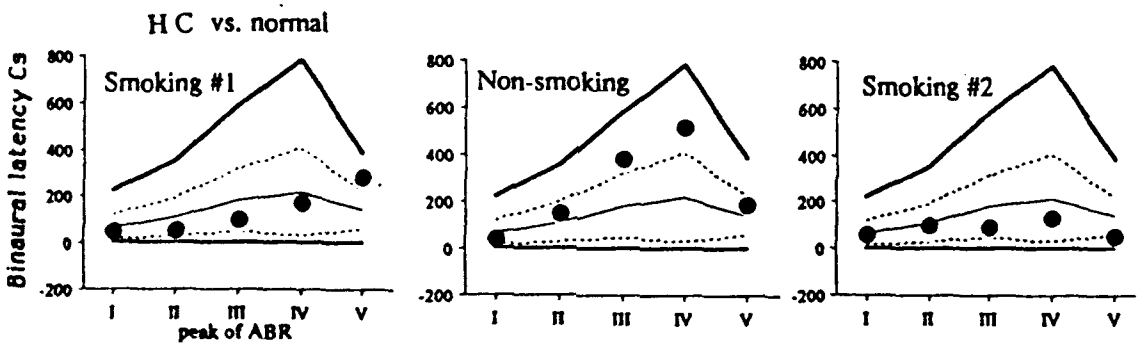

Figure R1. Individual (filled symbols) vs. group (background templates) data on Auditory Brainstem Response (ABR) latency stability for five vertex-positive peaks tested under binaural stimulation conditions. The individual scores are for subject HR. The group data represent a number of subjects similar in age to HR, and are summarized here in terms of the mean (fine solid line), +/- one standard deviation (two dotted lines), and +/- three s.d.'s (two heavy lines). Three panels represent HR's three sessions, the first and third while smoking, and the second during abstinence from cigarettes.

Figure R2 highlights the same effect by focusing only on the change in latency stability of peaks III and IV as a function of session (+/- substance use). We have adopted the term "smoker's needle" to refer to this effect, a term suggested by the protrusion of the latency-stability bars through the 1-s.d. "ceiling" of normality as shown in this form of the data. Thus the data suggest a neurological condition, indexed by ABR-latency hyperstability during abstinence, which seems to be resolved (i.e., the value of the index returns to normal limits) only when the subject is using the substance of choice.

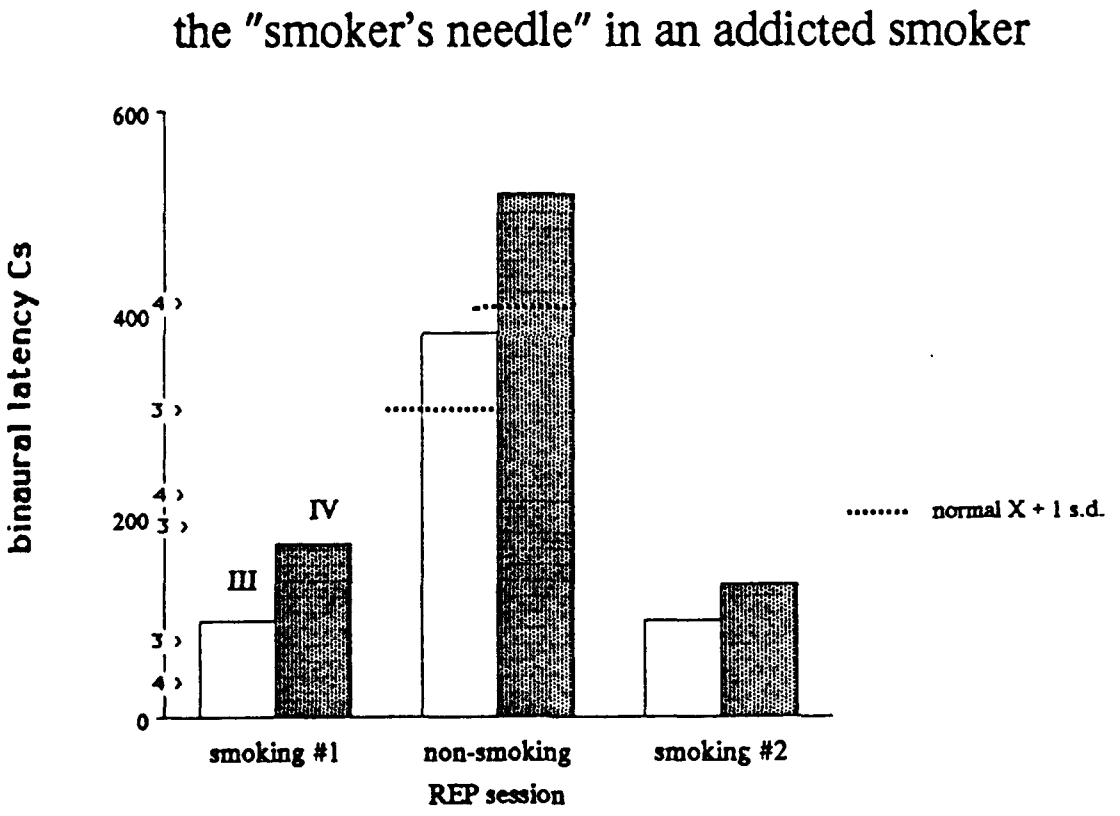

Figure R2. Bar-graph representation of selected data from Fig. R1: binaural latency stability for ABR peaks III and IV, as they occurred in the three test sessions for subject HR, during smoking (sessions #1, 3) and abstinence (session #2). The dotted lines indicate mean + 1 s.d. (cf. Fig. R1).

Figure R3 illustrates the effects on this subject's peak III and IV latency stability of the "stress test" incorporated in the REPs protocol (see MS paper for details): 1) during the first smoking session, the stability of both peaks is unaffected by the "stress test," that is, stability is equally low and normal for both sets of 4-binaural waveforms; 2) in the abstaining session, the stress test "breaks down" this hypothetically marginal system into its "second mode," mimicking the effect of cigarettes observed in sessions 1 and 3 by bringing the abstaining hyperstability down to within normal limits; and 3) during the final smoking session, the stress test again "breaks down" the system, again into the opposite mode, this time in a direction mimicking abstinence. Thus it appears that, if abstinence hyperstability is in fact a sign of a pre-existing neurological condition which is being self-medicated via use of a particular substance, the REPs "stress test" can mimic the effect of the substance on the system. Thus it may be possible that, in a single REPs session collected during abstinence from a substance, one can observe both the sign of the pre-existing condition as well as effects on that sign which are identical to the effects of the substance of choice.

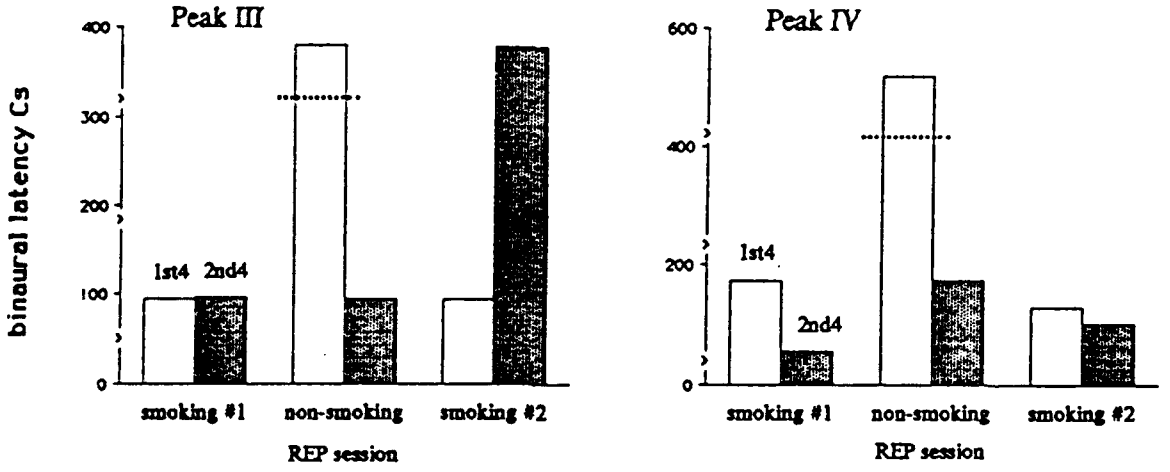

Figure R3. Effects on the "smoker's needle" (cf. Fig. R2) of the "stress test" incorporated in the REPs/ABR protocol. Note that in some cases, the "stress test" can serve to evoke the "other mode" of response in this system, either a reduction in stability (similar to the effects of substance use), or an increase in stability (mimicking system response during abstinence).

Results for the "non-addicted" husband (PR) corroborate these conclusions by providing an opposite effect. Comparison of his data with normals is presented in Fig. R4, and the "smoker's needle" suggested here for peaks II and III is highlighted in Fig. R5, where abnormal values appear -- in contrast to his wife -- ONLY IN THOSE SESSIONS WHILE HE IS SMOKING. This subject's latency stability is within normal limits only when he is not smoking. Thus these data suggest that, compared with his wife, this man is a "recreational smoker," with no pre-existing neurological condition: to the contrary, he induces an abnormality by using cigarettes.

The effects of the REPs stress test on his latency stability values are presented in Fig. R6, again illustrating the capability of this simple test to evoke one of two modes in a particular system.

In summary, the data from these two people corroborated their self report that they were opposite in their experience with cigarettes: one seems to be using cigarettes to resolve a (pre-existing?) abnormality, while the second employs cigarettes for another reason. Thus the results of the experiment provided evidence for the two subjects that the difference they perceived in themselves vis-a-vis cigarettes was "not in their minds, but in their brains." In follow-up interviews, it was learned that the woman had been diagnosed as hyperactive while in pre-school, and treated successfully with Ritalin. When she discontinued Ritalin upon entering junior high, she reportedly tried a variety of substances before settling on cigarettes as the best solution to her continuing hyperactive-like symptoms of restlessness, irritability, and reduced attention span. Thus the interpretation of the REPs findings in these two subjects seemed to be validated by their contrasting relevant medical history. This connection further suggests that the "smoker's needle" might be observed in at least some hyperactive children, where it could perhaps even prove to be a predictor of which children will require pharmaceutical (as opposed to behavioral?) intervention.

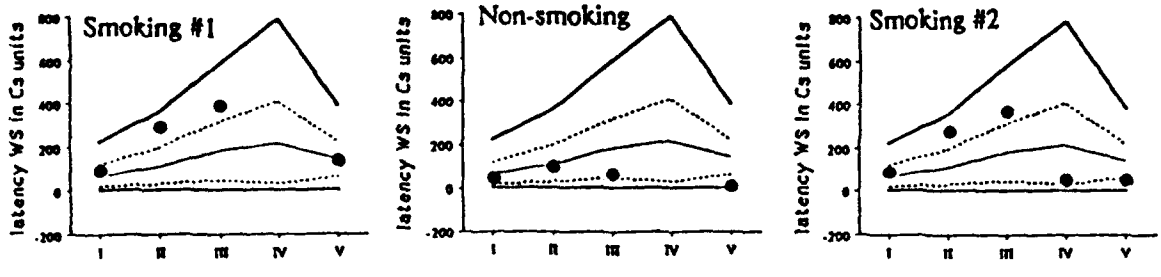

Figure R4. Comparison of PR's individual data on ABR binaural latency stability (filled symbols) with age-matched normals (background templates) [cf. Fig. R1].

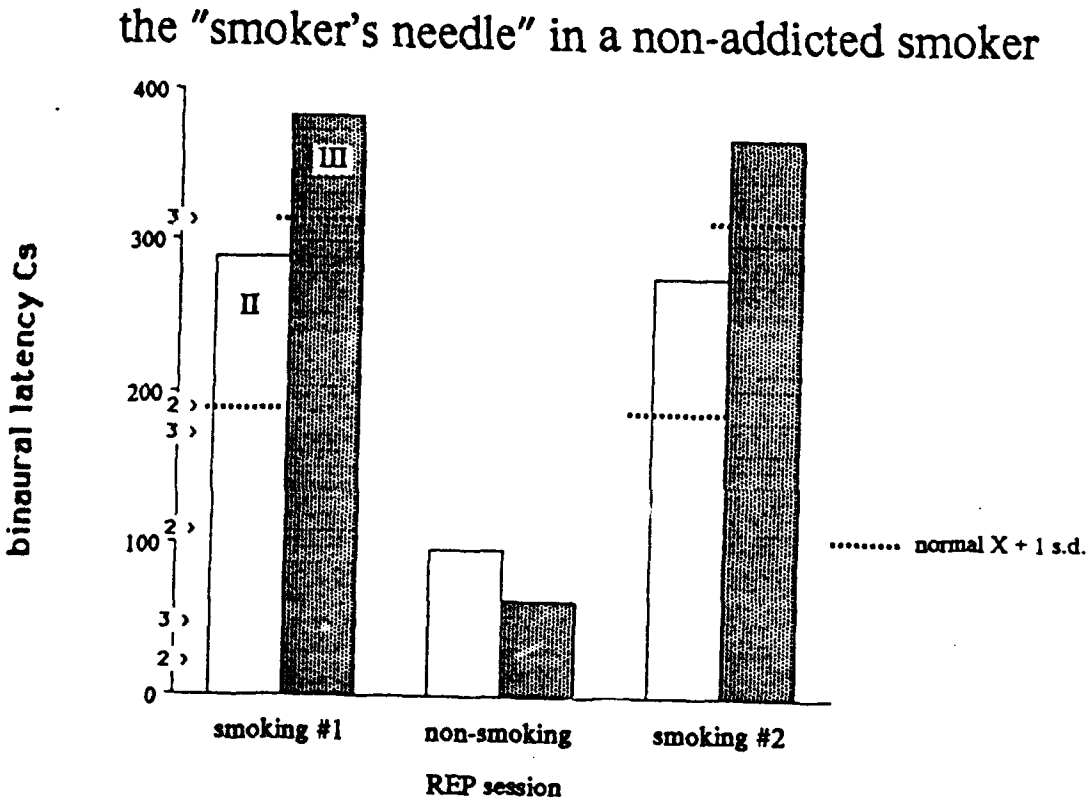

Figure R5. The "smoker's needle" (cf. Fig. R2) in non-addicted smoker PR, during three sessions, two during smoking (sessions #1 and 3), and one during abstinence from cigarettes (sessions #2). Note the effects are "equal and opposite" to those observed for HR (Fig. R2).

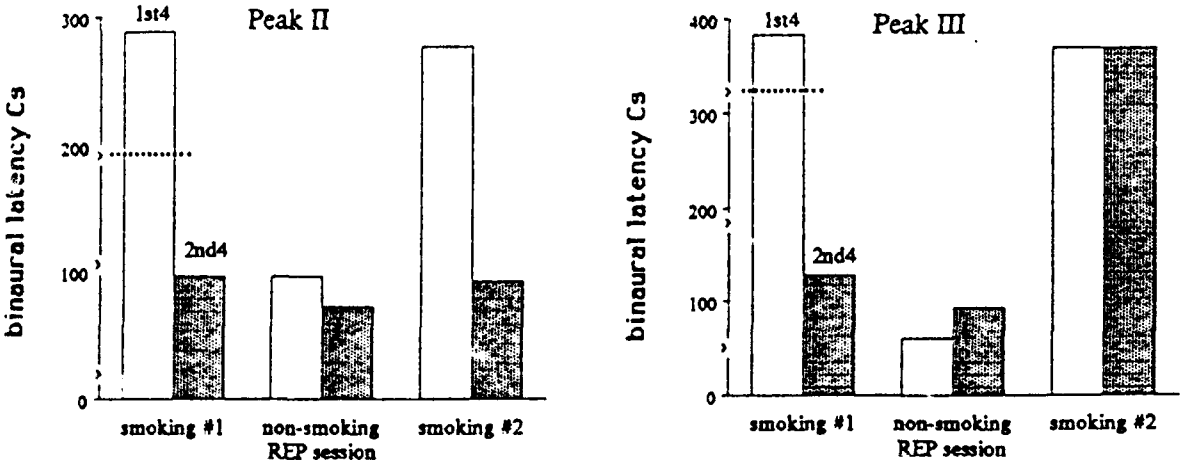

Figure R6. Effects of the REPs/ABR "stress test" on subject PR's "smoker's needle." Note the parallels between this test's results for PR, and for HR (Fig. R3).

Obviously these findings based only on HR and PR provide only very preliminary results. Many more within-subject studies of "addicted" vs. "recreational" users must be conducted before a sophisticated interpretation of the significance of ABR hyperstability may be made. However, some additional REPs/ABR data are available for a small number of individuals with a history of addiction to a variety of substances, from hard drugs to cigarettes and alcohol.

All of these individuals were tested in a single REPs/ABR session conducted in a period of recovery with complete abstinence; some were tested only a few weeks after cessation of substance use, while others were tested during a recovery period representing several years' abstinence. In all those tested, the "smoker's needle" was observed, and, as with HR and PR, was indexed by binaural latency hyperstability involving ABR peaks II, III, and/or IV.

Results for three additional subjects, showing the "smoker's needle," with effects of the "stress test" for each, are presented in Figs. R7 - R9. Findings for this variety of subjects suggest that the "smoker's needle" may be "treated" with a number of substances; it is further possible that a more complete understanding of this brainstem sign and its neurological context (cf. second report below) may help in distinguishing among populations of substance abusers, and perhaps eventually provide guidelines for identifying a neurological substrate for the concept of "substance of choice."

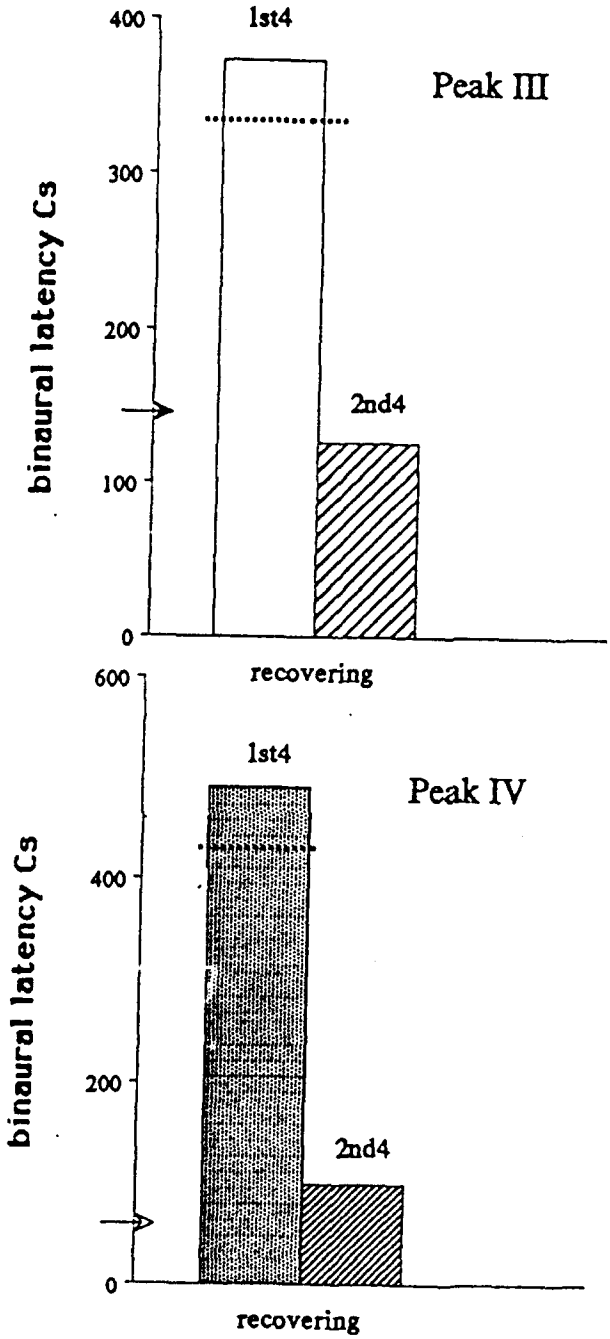

Figure R7. "Smoker's needle" and the effects of the REPs/ABR "stress test" in MH (female, age 26) who reported use of a variety of drugs including alcohol and cigarettes starting at age 14; tested at 2 years 5 months abstinence from all substances.

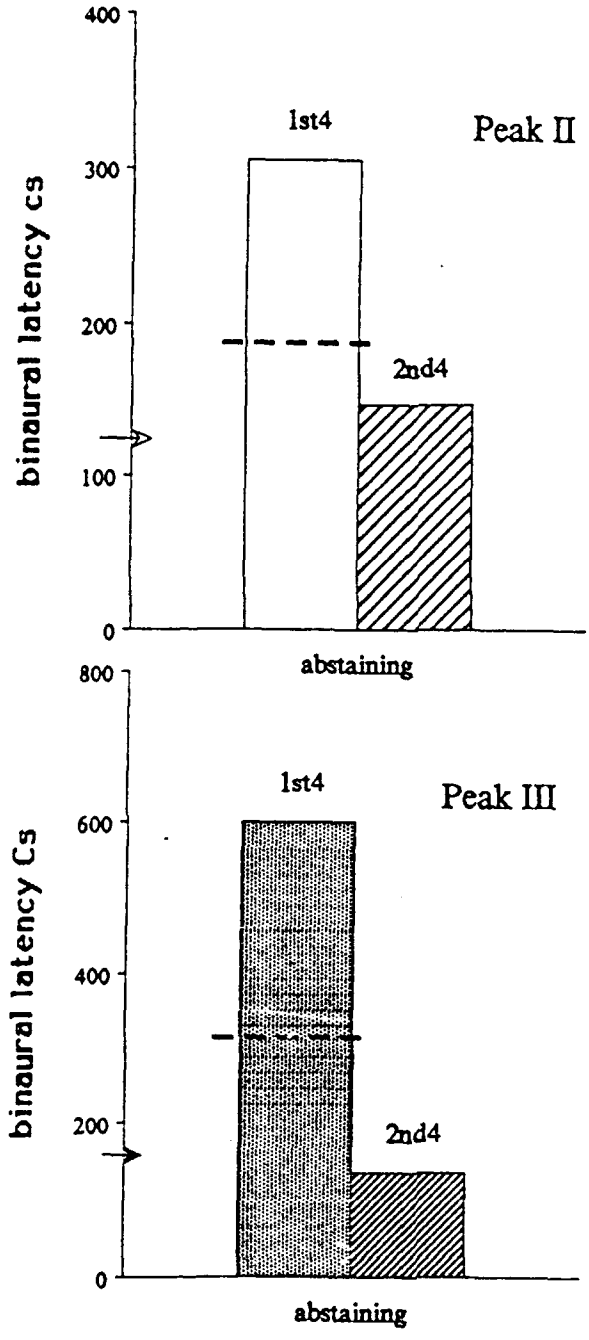

Figure R8. "Smoker's needle" and the effects of the REPs/ABR "stress test" in JW (male, age 48) who reported use of a variety of drugs including cigarettes, alcohol, marijuana, and hashish starting at age 15; tested at 8 years abstinent from all but cigarettes, and at 1 week abstinent from cigarettes.

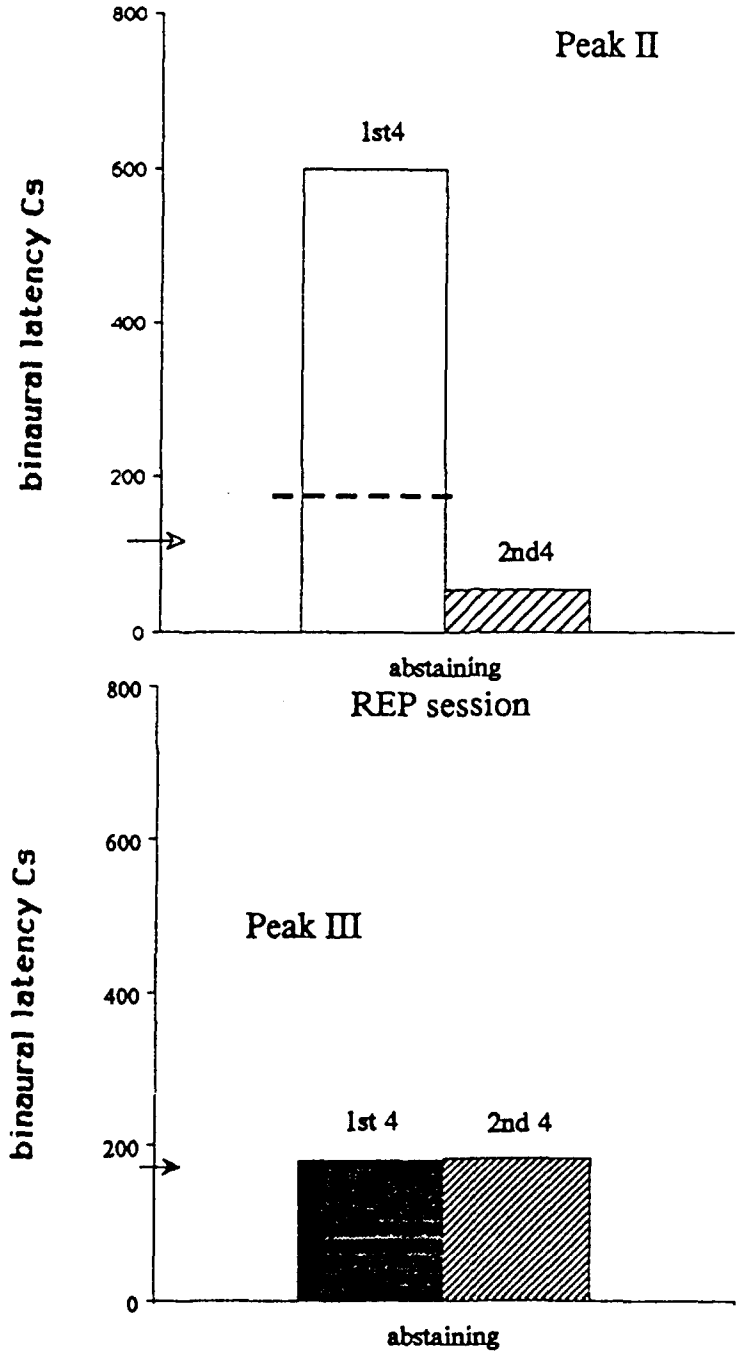

Figure R9. "Smoker's needle" and the effects of the REPs/ABR "stress test" in CJS (female, age 35) who reported using cigarettes for a number of years; tested at 9 years' abstinence.

UNPUBLISHED REPORT #2

Lauter, J.L. (1991) "qEEG correlates of the 'smoker's needle:' Observations in an addicted smoker with a history of hyperactivity treated successfully with Ritalin"

Questions regarding the "neurological context" of the ABR hyperstability effect termed the "smoker's needle" observed under different conditions in two subjects HR and PR (see first report, above) led to a corollary series of experiments on these same two individuals. Approximately one year following the first three-session series, HR and PR were recruited to take part in a similar "on-off-on"series, in which data for both REPs/ABR and resting qEEG measurements were collected. The experiment was conducted on a collaborative basis with Dr. Gerald Senf, using a Cadwell Spectrum 32 qEEG system housed in his private-practice Brain Map Labs in Tucson AZ.

The original plan for the second series was to test both subjects during abstinence from cigarettes, accompanied by an on-off-on schedule with Ritalin, which in the intervening year had been prescribed for HR by a local pediatrician specializing in hyperactivity. This doctor also agreed to prescribe Ritalin, under supervision, for PR, in the interest of our planned experimental series. When both individuals sampled the Ritalin, PR found it only made him feel "mildly happy," but HR reported that in her, it produced an extreme allergic reaction (a crippling degree of water retention in her feet).

Thus it was decided to test PR under the planned protocol (on-off-on Ritalin), and to test HR under a simple replication of the schedule used one year previously: on-off-on cigarettes. The schedule for the REPs/ABR + qEEG test series was as follows. For HR, one session while smoking, a second session at least one week later and at least 3 days after cessation of smoking, and a second session at least one week later under either smoking condition. Her husband PR was requested to abstain from cigarettes for all three sessions, and to take a small dose of Ritalin one hour before the first and third sessions.

Dependent variables included: 1) mean and stability of latency and amplitude of each of the first five vertex-positive peaks in the 16 REPs waveforms collected from each subject in each session; and 2) delta coherence comparing electrode locations T3 and T4 calculated by the Cadwell Spectrum 32 system for an artifact-free 2.5 minutes of EEG collected during resting conditions (eyes closed, room darkened).

Data collection for both HR and PR has been completed, but only results for HR's qEEG measures are available as of 12/91. Findings for PR will be included in a later report.

Results: HR. It is expected that the "smoker's needle" effect in ABR binaural

latency stability seen previously in HR (see first REPs report from 1990, above) will be replicated in this series (cf. similar observations by Lauter and Lord-Maes, 1990); however, since analysis of the 1991 results is not complete, the ABR data from 1990 are used here as a hypothetical comparison with the observed qEEG changes from the 1991 series (Fig. R10, data indicated by bars). Over the course of the three similar sessions in 1991, an "equal and opposite" change in qEEG delta coherence was measured at T3/4 (Fig. R10, data indicted by lines). The coherence data from HR measured in 1990 are included at the left for a comparison.

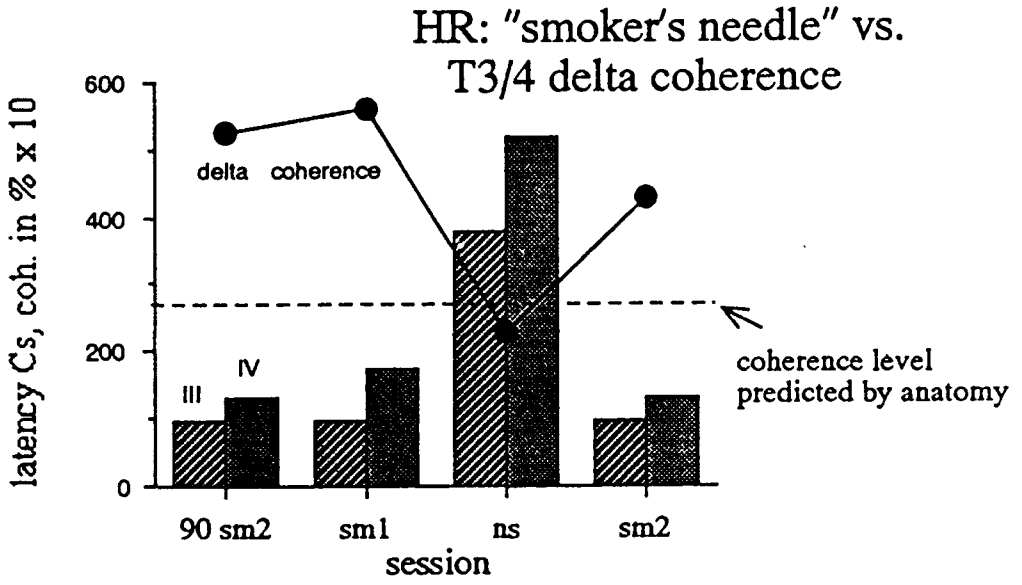

Figure R10. Comparison of changes in ABR binaural stability (bars) vs. T3/4 delta coherence measured during resting conditions (line) as a function of change in session status, whether during a smoking period (sessions #1, 3) or abstinence (session #2).

Note the good degree of replication over one year's time of the level of resting T3/4 delta coherence in this subject. Also indicated on the graph is an estimate of the coherence level which would be predicted based on HR's periSylvian asymmetry; if this predicted value is taken as a guide, it is clear that the level of coherence observed during smoking sessions is actually a "hypercoherence," which changes to approach the predicted value (i.e., becomes more "normal") during abstinence (when the brainstem hyperstability appears), and moves back toward "hypercoherence" (accompanied by normalization of the brainstem measure) with resumption of smoking.

The increased coherence observed in this subject during smoking sessions recalls an observation made by Elbert & Birbaumer that "nicotine improves interhemispheric coordination" (Elbert & Birbaumer 1984, p. 195). These authors also hypothesized that "transmission of information between brain hemispheres might be imapired in deprived smokers and...nicotine helps to compensate for this regulation deficit" (p. 195). It is possible that our observations in HR corroborate this observation, in that this subject's coherence is dramatically increased while she is smoking (perhaps a physiological sign of 'improved interhemispheric coordination' induced by nicotine), and assumes a lower value when she is abstaining from cigarettes.

However, the fact that HR's "increased coherence" is actually a hypercoherence (i.e., higher than would be predicted based on the underlying anatomy), combined with the way in which our measure of ABR stability covaries with delta coherence, suggests a subcortical corollary to observations regarding the cortical effects of nicotine. The corollary invokes the hierarchical functional physiology of the central nervous system according to which higher levels of the system act to modulate the activity of lower levels: cf. peripheral spasticity resulting from damage to upper motor neurons (UMNs).

The hypothesis relevant to the case of substance addiction is that there is in fact a crucial "normal" balance in terms of physiological activity that must be maintained between levels of the system, and that this balance may be disrupted in at least two ways: hypoactivity of upper levels (as in UMN disease), or hyperactivity of some sort originating at lower levels. It is further posited that either type of dysfunction could give rise to an observation of hyperactivity at a lower level, such that in Jacksonian terms, lower-level hyperactivity deriving from a lower-level abnormality would be an example of an "irritative effect," while lower-level hyperactivity deriving from an upper-level abnormality would be a "release effect." Thus, only by observing characteristics at several levels can one distinguish the focus of the abnormality, i.e., whether affecting top-down modulators, or lower input centers.

Given this reasoning, the combination of ABR and qEEG findings in HR suggest the existence of a neurophysiological abnormality at the brainstem level which may have predated her use of cigarettes. Thus it may be this brainstem abnormality which accounted for the hyperactivity she experienced as a child, and for the continuing similar symptoms which she reports as an adult, all of which are very much in keeping with concepts of brainstem functions regarding arousal.

In conclusion, the ABR hyperstability which we have referred to as the "smoker's needle" may be either a primary or a secondary sign of the brainstem dysfunction giving rise to these symptoms, and it is possible that the Ritalin which HR was prescribed as a child, and the cigarettes she uses as an adult, both serve to ameliorate the effects of the abnormality. It is further hypothesized that at least in this subject,

these substances act indirectly on the brainstem physiological abnormality by increasing top-down modulation in some way (indexed by increased delta coherence recorded over the cortex) to a level which is sufficient to "turn down" the hyperstability at the brainstem level. The key to placing HR's abnormality in the brainstem is the fact that in order to bring ABR stability into a normal range, she must induce cortical hypercoherence (i.e., compared to a level predicted by the underlying anatomy).

Further conclusions about the generality of these findings and their connection with etiology perforce wait on many more studies of individuals with a variety of types of substance abuse and perhaps other addictions. In order to make progress toward more sophisticated diagnosis, identification of cause, and therapeutic interventions, such studies must be based on obtaining as much information about each individual as possible, including personal and family medical history as well as multiple test methods employed in within-subject designs. Only in this way will we be able to meaningfully explore all facets of these debilitating and socially disastrous disorders.

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Repeated-measures auditory brainstem responses (ABRs): comparisons of stability profiles based on different time schedules. Judith L. Lauter and Jan Lord-Maes (Department of Speech & Hearing Sciences, University of Arizona, Tucson, AZ 85721)

ABSTRACT

Demonstrations of dramatically increased information from ABRs based on variability analysis [J. L. Lauter & R. L. Loomis, Scand. Audiol. 15, 167-172 (1986) and 17, 87-92 (1988); J. L. Lauter & R. G. Karzon, Scand. Audiol. In Press a, b, c] have to date all been based on within-subject series of weekly test sessions. Toward making repeated-measures EPs more feasible as a research and clinical tool, the current experiment compares ABR stability profiles based on different test schedules: four waveforms per ear of presentation collected from each subject with 1) minimal separation between ear sets (i.e., 4 right-ear, left-ear, and binaural waveforms, all collected within the same 1-hour session), 2) one-hour separation between ear sets, and 3) one-week separation between ear sets. Results to date indicate: 1) very good matches between stability profiles based on same-session vs. weekly collections, validating an earlier claim that these profiles reflect real individual characteristics; and 2) distinctions between profiles from these two schedules vs. the hourly collections, possibly reflecting the influence of diurnal variations in auditory EPs reported by earlier researchers [G. A. Kerkhof et. al., Neurosci. Lett. 16, 11-15 (1980)].

INTRODUCTION

Our previous work with repeated-measures ABRs indicates that there is much more information to be gained from these easily-collected responses than is revealed by simple single-waveform measures of latency and amplitude. Employing clinically standard testing and analysis procedures, with the sole modification the use of a repeated-measures design, we have demonstrated that a simple measure of peak stability, applied to both latency and amplitude measures, reveals individual differences between subjects, differences due to ear of stimulation, and differences correlated with age (see references for a complete list of papers and presentations).

All of these results were obtained with series of weekly test sessions. In order to render repeated-measures EPs more feasible as a tool for a range of potential basic-research as well as clinical applications, we here report results of a within-subject examination of the patterns of ABR peak latency stability measured according to three test schedules: 1) weekly (one left-ear, right-ear, and binaural waveform collected from each subject once in each of four weeks--similar to our earlier studies), 2) hourly (one waveform for all three ear conditions collected one hour apart for a total of four collections per half-day), and 3) "back to back" (four left-ear waveforms followed by four right-ear waveforms, then four binaural waveforms, collected in the same 1.5-hr session). We wished to observe not only whether there were distinctions in the absolute level of stability across the three time schedules (i.e., would four waveforms per ear collected in the same session show greater stability than if a week intervened between the waveforms?), but also to what extent the individual patterns of stability observed for each ear condition in each subject were replicated across the three time schedules.

METHODS

Subjects were eight adults, four females and four males, ranging in age from 15 to 45 years. All were neurologically normal by report, and were screened for normal hearing prior to ABR scheduling. Each subject was scheduled for a total of five ABR sessions (Fig. 1): four weekly sessions, scheduled for the same day of the week, same time of day, followed by a single half-day session, usually scheduled for the Saturday following completion of the last weekly session. On each weekly test session, one 2000-sweep waveform for each of left-ear, right-ear, and binaural presentation conditions was collected, to serve as the four-waveform-per-ear "weekly" data series; on the last weekly session, an additional three waveforms for each of the conditions was collected, so that these four within-session waveforms for each ear served as the "back to back" series; and on the concluding half-day, one waveform each for the three conditions was collected at hourly intervals, to form the four-waveform-per-ear "hourly" series.

Procedures and equipment were similar to those used in our previous studies (see references for details); all aspects of subject preparation and test design were clinically standard. The experiment was conducted on a Nicolet CA-2000 system, and waveforms were collected to presentations of 100 usec condensation clicks played at 11.1/sec at 80 dB nHL, via system filters set at 150-3,000 Hz (-3dB) for inut from 9-mm silver disk electrodes placed at vertex, earlobes, and forehead.

Waveforms were stored on floppy disk for off-line analysis, which consisted of determining the position of each of the first five vertex-positive peaks, and recording both latency and amplitude of each. Following the practice established in our earlier experiments, the mean and standard deviation of these values were determined for the following combinations: 1) between subjects (mean and s.d. computed over subjects separately for each peak x ear combination based on weekly, hourly, and back-to-back waveform #1, then #2, then #3, then #4, and then the ratio of mean divided by s.d. ("Coefficient of stability") was computed for each of these combinations, and all four values per time schedule averaged to determine the "mean between-subject Cs" for that time schedule; 2) within subjects (each individual's mean and s.d. computed over all four waveforms per ear per time schedule, the Cs ratios were computed, and then these ratios were averaged across subjects to give a "mean within-subjects Cs" for each peak x ear x time schedule. Similar calculations were also done for individual subjects, so that we could observe the within-subject agreement in ABR latency stability patterns across the different test schedules.

RESULTS

Group calculations. As expected, for the most part, absolute latencies did not reflect either subject differences, ear differences, or schedule differences (Fig. 2). There was a small time x peak interaction, accounted for by a significantly shorter latency for peaks I and II collected in the back-to-back series versus the other two schedules ($p < .05$ for both).

Between-subjects stability values (Fig. 3) showed no differences due to schedule. Tested with a three-way ANOVA (time x peak x ear), there was an interaction in these values for peak x ear ($p < .01$) [a Neuman-Keuls test indicated that the right-ear BS Cs was larger than the other two for peak I, but smaller than the other two for peaks IV and V], and a main effect for peak ($p < .01$) [BS Cs values are generally

highest for peak V, next highest for III and IV, and lowest for peaks I and II]. The peak differences for the right-ear response are peculiar to this group of subjects, and reflect the sensitivity of the stability measure, even when calculated for groups, to the characteristics of the individuals comprising the group. The main effect for peak suggests that as a group, these individuals become more homogenous in peak latency as one ascends the auditory system. Again, this effect is not seen in every group tested.

When graphed, the within-subject stability values (Fig. 4) showed a number of apparent differences. Tested with an ANOVA, these apparent differences were documented as main effects for both peak and time. Specifically, peak III showed the highest stability (Neuman-Keuls, $p < .01$), and WS latency stability was significantly higher for the back-to-back schedule than for either of the other two series (Neuman-Keuls, $p < .01$).

We also tested the BS and WS values for each time schedule separately, to compare with our previous reports. For all three time series, WS stability (cf. Fig. 4) was significantly greater than BS (cf. Fig. 3): for the weekly series, a Neuman-Keuls test indicated that this difference was significant at the .05 level; for the hourly and the back-to-back series, the difference was significant at .01.

Individual differences. Mean and standard deviations were also measured for each individual's time x peak x ear combinations, and latency Cs values calculated for each. In many cases, we found that there was a good match between the latency-stability patterns based on the back-to-back and weekly schedules, with a different stability pattern for the hourly series (see examples in Fig. 5).

Note also that the general pattern revealed in the group ANOVAs of latency stability being higher for the back-to-back than for the weekly schedule, is reflected in these individual data; among those shown in Fig. 5, the difference is most striking for JL's binaural values, where the shape of her latency-stability profile favoring peak III is only vaguely suggested in the weekly data, but becomes dramatically enhanced in the back-to-back series.

DISCUSSION

These findings have clear implications for establishing the practicality of using repeated-measures EPs for basic research and clinical applications (examples in Fig. 6). Not only are all the patterns which we have observed earlier based on weekly schedules present in the profiles based on the back-to-back collections, but the clear within-subject similarities in profiles based on the two schedules, as well as the increased stability which in some cases enhances profile articulation, lead us to conclude that all of the details we have described previously in these measures based on weekly series will be available in within-session series.

For example, the age-related changes we have reported in ABR stability (see references for presentations) are observable not only in results from a (bi-)weekly series, but also in a within-session series. Our study of 10-12-year-old children (e.g., Oyler & Lauter 1989) included a within-subject comparison of profiles based on the two test schedules, and, as with the adults examined here, in many cases ABR stability profiles were not only replicated but often were enhanced going from weekly to within-session series.

Based on the current findings, we have begun data collection in several clinical populations, including individuals with Alzheimer's Disease, multiple sclerosis, and children with attentional and learning

disorders. The within-session design of repeated-measures ABRs consists of collection of 4 left-ear, 4 right-ear, and 8 binaural waveforms. Not only does this type of test schedule seem to be well-tolerated by both experimenter and subject, but data from one session can be analyzed in two to three hours. Early results on the individuals with multiple sclerosis are very encouraging regarding the sensitivity of ABR stability to stage and severity of this type of nervous-system disorder.

Finally, the similarity on the one hand between profiles based on weekly and back-to-back schedules, and on the other, the difference between profiles from these two schedules vs. hourly suggests that the scheduling arrangement was important: as indicated in Fig. 1, the back-to-back waveforms were collected at the last weekly session, thus representing the system studied at the same time of day on the same day of the week as used in the weekly series. In contrast, the hourly series was usually collected on a Saturday (since it required at least one-half day to complete), and usually in the morning. None of the subjects received weekly testing on Saturday, and most weekly sessions took place in the afternoon. Thus in general, the hourly waveforms represent the individual systems studied at a time that was different both in terms of time of day and day of the week than the weekly/back-to-back waveforms.

Kerkhof et al (1980) have described amplitude variations in cortical auditory EPs that seem to be related not only to time of day but also to self-rated alertness in "morning-" and "evening-type" subjects. It is possible that the observations in the current experiment regarding differences between ABR stability profiles collected at different times of day in the same subjects extends these earlier results, suggesting that diurnal variations may be expressed in brainstem responses, as well. The fact that we can see this apparent effect even in ABR latencies is a further testimonial to the sensitivity of the repeated-measures approach which emphasizes the stability rather than simple absolute values of EP waveform parameters.

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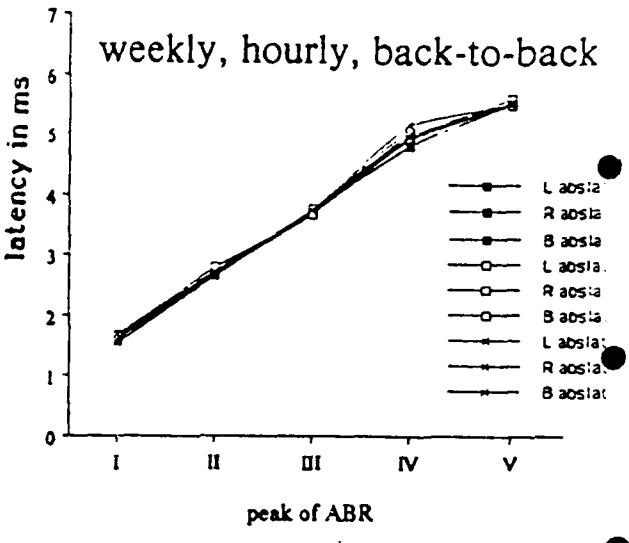
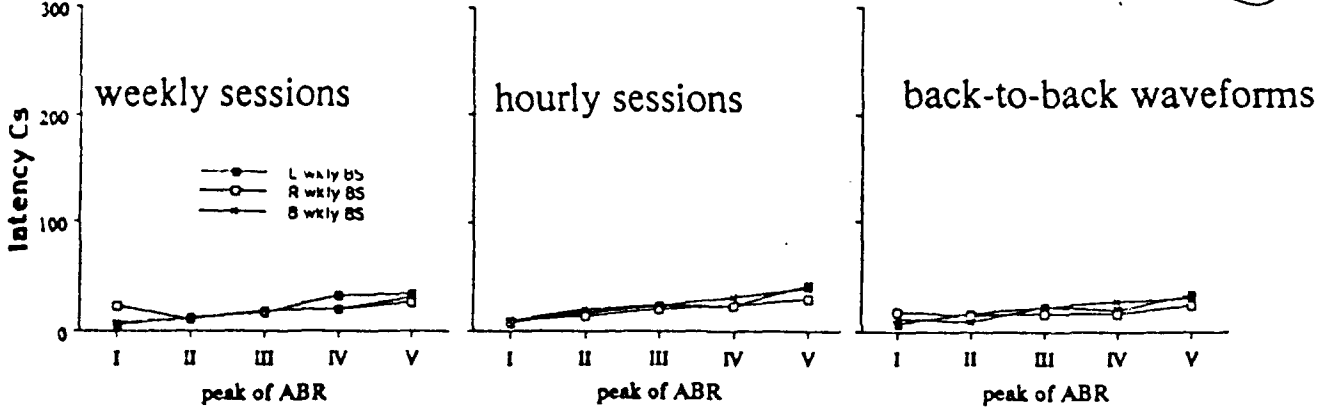
5-session schedule for a subject: (1)

Monday April 7	3 pm	1L, 1R, 1B	"weekly"
Monday April 14	3 pm	1L, 1R, 1B	
Monday April 21	3 pm	1L, 1R, 1B	
Monday April 28	3 pm	1L, 1R, 1B	"back to back"
		1L, 1R, 1B	
		1L, 1R, 1B	
		1L, 1R, 1B	
Saturday, May 3	8 am	1L, 1R, 1B	"hourly"
	9 am	1L, 1R, 1B	
	10 am	1L, 1R, 1B	
	11 am	1L, 1R, 1B	

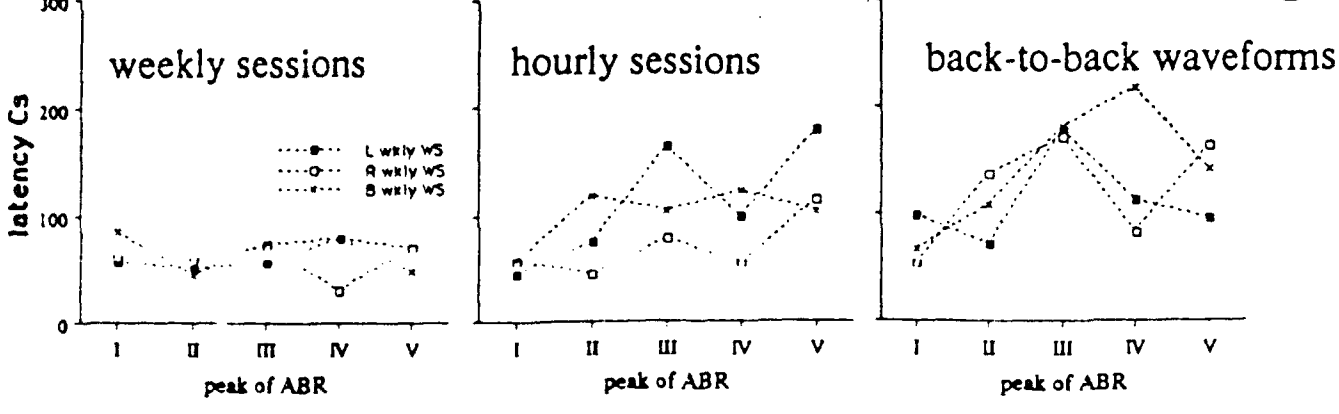
absolute latency (2)

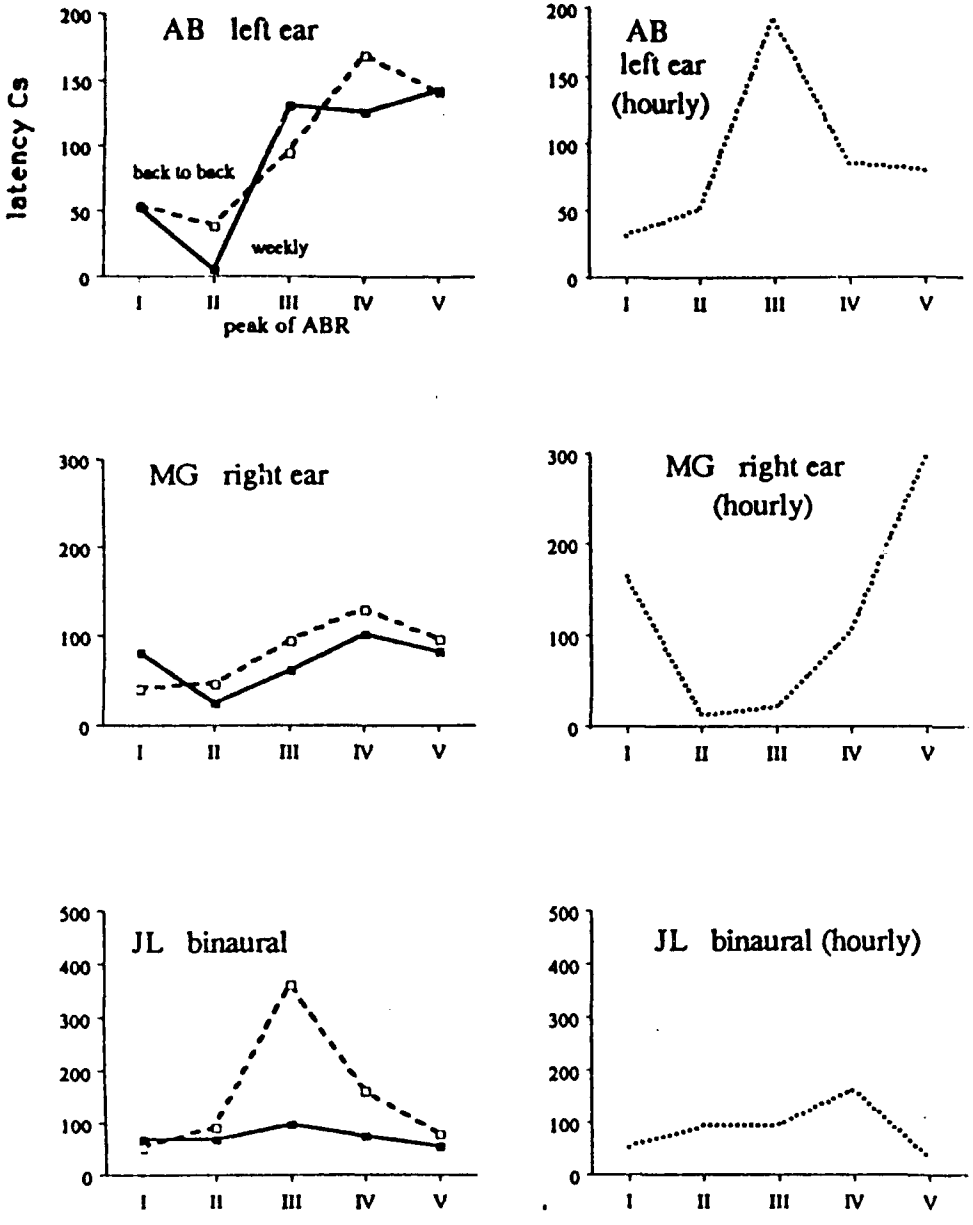


Between-subject latency stability (3)



Within-subject latency stability (4)





Applications for repeated-measures ABRs

1. biorhythms (hourly, daily)
2. parametric studies (level, filters, signal spectrum)
3. development and effects of ageing
4. clinical studies
   a. acute conditions (IOM; prognosis in coma)
   b. chronic conditions (CAD diagnostics; substance abuse/addictive behavior)
   c. progressive or fluctuating conditions (growth of acoustic tumor; early effects of ototoxic drugs; cycles and staging in multiple sclerosis)

Repeated-measures ABRs in multiple sclerosis: Demonstration of a new tool for individual neurological assessment. Judith L. Lauter and Janiece Lord-Maes (Dept. of Speech and Hearing Sciences, University of Arizona, Tucson AZ 85721) Abstract: J Acoust Soc Amer (1990) 88: S18.

ABSTRACT

Our research using a simple measure of evoked-potential variability based on repeated-measures within-subject testing has demonstrated that: 1) replicable patterns in relative variability both of latency and amplitude in peaks of the auditory brainstem response (ABR) may be observed in normal children and adults, and 2) these patterns are sensitive to individual differences, ear differences, and developmental changes persisting at least through age 12. Several individuals with multiple sclerosis have now been tested using our protocol, based on clinically-standard procedures for data collection and analysis, with the single exception the repeated-measures design, comprising collection of four left-ear, four right-ear, and eight binaural waveforms in the same 1.5-hour session. Results to date indicate that the array of dependent variables yielded by this method: 1) may distinguish MS patients from normals as well as from members of other groups such as Alzheimer's patients and substance abusers; and 2) makes it possible to order MS patients along a continuous scale from mild to severe, in a ranking which compares well with clinical ratings. We are currently extending these observations to include other progressive diseases such as Alzheimer's Disease and Parkinsonism, and pathologies involving arousal, such as addictive personality, hyperactivity, and coma. Indications promise new applications in differential diagnosis, disorder staging (acute status, progressive time course, cycles of remission and exacerbation, etc.), and objective documentation of treatment efficacy.

INTRODUCTION

Over the past several years, we have reported to this Society a series of experiments illustrating the dramatic increase in information available from standard evoked-potential tests when measures of the variation of waveform parameters such as latency and amplitude are added to conventional observations of the absolute values of these parameters. (For reports and publications, see references.) The required protocol is termed Repeated Evoked Potentials (REPs), stressing that the strategy is applicable to any type of evoked potential, although our research has focused on auditory stimulation and within this, primarily on study of the auditory brainstem response (ABR). The goal of the REP strategy can be summarized as the study of systematic variation, i.e., that which occurs over and above the noise floor inherent in EP testing, such as variability due to earphone slippage during the same session, replacement of electrodes in separate sessions, changes in equipment, differences in peak-picking criteria from experimenter to experimenter, etc. We have shown that the patterns of ABR relative stability can be observed in spite of fluctuations in these sources of ABR variability, and that the patterns reveal a number of aspects which are invisible in conventional ABR measures (see below).

The study of systematic variation in EPs is analogous to certain types of clinical research in speech motor control in which the variability of production within individual patients is studied in order to characterize individual expressions of a disorder, to examine progression (or remission with therapy) of a disorder, and to

differentiate patients not only from normals but also from other clinical groups. Our own focus in the REPs testing has been on within- as well as between-subject details: in the first category, we have demonstrated ear differences, differences in the degree of stability from level to level in the auditory CNS, distinctions related to change of state (such as circadian rhythms), and good replicability of these "fingerprint" stability profiles over time; in the second, we have described individual differences, distinctions in the degree of homogeneity of subject groups, and developmental changes occurring in the auditory brainstem as late as 12 years of age. Parameters of interest have included both the latency and amplitude of waveform peaks; we have shown that although amplitude is approximately one order of magnitude less stable than latency, there are still systematic and replicable patterns to be observed in peak amplitude at all levels in the auditory evoked response. The measure of stability we use is termed the Coefficient of Stability (mean divided by standard deviation). This is the reciprocal of Pearson's Coefficient of Variability, and was chosen to emphasize stability in that the value of the ratio varies inversely rather than directly with standard deviation.

MULTIPLE SCLEROSIS AND REP/ABR: CROSS-SECTIONAL STUDY

Our REP research to date has focused on the study of neurologically normal individuals, using multiple waveforms collected in weekly sessions. Based on a study reported to this Society last spring (Lauter & Lord-Maes, 1990) in which we demonstrated that the same types of patterns could be observed in multiple waveforms collected in the same session, we have now modified the REP/ABR protocol for use in clinical applications. The test schedule involves a single 1.5-hr. session (multiple sessions are required only for longitudinal studies), during which 16 waveforms are collected: 4 with left-ear, 4 with right-ear, and 8 with binaural stimulation. The 8 binaural waveforms provide us not only with a 4-waveform binaural condition to compare with the two monaurals, but also with a test-retest comparison (1st 4 binaurals vs. 2nd 4), which most often reveals either no change or an increase in response stability in normals, in contrast to a decrease in stability in compromised systems such as in individuals with multiple sclerosis. Thus the collection of 8 sequential binaural waveforms amounts to a "stress test," analogous to exercise stressing in cardiology or the "hot bath" test used in neurology to bring out symptoms which may be otherwise invisible.

Test parameters are chosen from standard clinical operating procedures for ABRs: electrodes at Cz (active), A1 and A2 (reference), and Fpz (ground); monaural conditions referenced to both ipsilateral and contralateral earlobes and binaural referenced to linked earlobes; 100-us condensation clicks presented at 80 dB nHL at a rate of 11.1/sec; 2,000 responses per waveform collected via filters set at 150 to 3000 Hz using a Nicolet CA-2000 system. Peaks are selected by eye using a screen cursor, and latency and amplitude values are provided by the system. For each individual subject, these values are then entered into matrices providing for display of actual latency (page one) and amplitude (page two) of each peak tested under each ear condition: each table thus has 15 columns (5 peaks x 3 ears) and 4 rows (four waveforms for each ear condition). A second set of 4 rows in each table records values for the five peaks in the second set of 4 binaural waveforms. Mean and standard deviation of latency and amplitude are then calculated over the first four waveforms for each condition, and combined to yield the Coefficient of Stability (X/s.d.). Mean, standard deviation, and Cs are also calculated for each peak for the second set of binaural waveforms.

Based on these calculations, each individual is then characterized by graphical displays of four measures:

absolute latency, absolute amplitude, latency stability, and amplitude stability, all compared against a database of age-matched normals (see Fig. 1 for an example for one multiple-sclerosis subject's left-ear data). In these displays, individual data are represented by the large filled circles, and the normal data are indicated in terms of mean (fine line), plus/minus one standard deviation (dotted lines), and plus/minus three standard deviations (heavy lines). Then each of the individual's data points is judged relative to normal, e.g., this subject's Left-ear Peak I absolute latency is more than one standard deviation late relative to normal, and his Left-ear Peak V latency stability is equal to three standard deviations higher than normal (an instance of "hyperstability," clearly a pathological sign in some populations).

A tally of these deviations from normal can be summarized in a "REP score table" (Fig. 2), which is a matrix of peak (columns) by ear (rows). The entries can be collapsed over ears to show distribution of abnormalities by peak (matrix section labelled TOTALS), or by ear (matrix section labelled REP Totals), and a final characterization of the subject in terms of the number of scores which were "late or low" (late latency or low amplitude, latency stability, or amplitude stability compared with normals) and those which were "early/high" (early latency or high amplitude, latency stability, or amplitude stability compared with normals). The subject whose data are shown in Fig. 2 is characterized as "50 late/low, 2 early/high" [note that summaries are based on use of a weighting for all those scores which are equal to or greater than 3 standard deviations from normal, accomplished simply by multiplying the number of these instances by 2].

Figure 3 Panel A displays a graphical representation of this subject's REP scores by peak, showing fairly even distribution of the late/low scores across all five peaks, with the single occurrence of a "high" value at peak V. This pattern is contrasted with a very different one in Panel B representing a second MS patient.

Figure 4 presents a summary of the late/low vs. early/high scores in a group of 13 individuals with MS, recruited from a single neurological practice at the University of Arizona Medical Center in Tucson. Individuals were tested and their ABR data analyzed with the experimenters blind to the patients' clinical status. Based solely on the results of the 1.5-hr ABR session and the REP-score analysis described above, subjects were then ordered from most mild (on the left in this graph) to most severe (on the right) according to the number of late/low REP scores for each (filled symbols)-- as it turned out, their ranking based on early/high scores (open symbols) varied inversely with the late/low ranking. In Fig. 4, data points for individual subjects are joined to indicate that the graph's abscissa not only represents a cross-sectional ranking of individuals in a population, but also a hypothesized dimension of severity: for example, it is predicted that if subject RLB were followed over time with a sequence of REP/ABR sessions, her late/low and early/high scores would follow approximately the same functions as defined here for the group: the number of early/high scores declining over time, and the number of late/low scores increasing as the disease progressed.

The REP/ABR ranking of the 13 subjects was then compared with the attending neurologist's ranking based on general clinical status. Results are presented in Fig. 5, indicating an excellent match between the two rank orderings of these individuals: in only two instances was the neurologist's ranking milder than that based on REP/ABR (subjects LBBM and VS--perhaps indicating that demyelination was more severe in the brainstem than in those systems observed in clinical testing, or that the REP test was more sensitive than clinical tests), and only one subject was judged more severe by the neurologist (RA--perhaps hinting that demyelination had not advanced in the brainstem to the extent that it had affected other systems).

MS AND REP/ABR: LONGITUDINAL STUDY

Finally, we have one brief case history testing the hypothesis that the abscissa of Fig. 4 describes a dimension of within-subject severity. A subject from another neurologist's practice agreed to schedule two REP/ABR sessions approximately 6 weeks apart. Between the two sessions she kept a daily log tracking her own evaluation of her clinical status on some 50 features, such as spasticity, depression, occurrence of blind spots, etc., each ranked daily according to a 6-point scale (6 for very good status, 0 for poor). In Fig. 6 is illustrated a range of degree of fluctuation in different features, contrasting spasticity (high day-to-day fluctuation in judged severity) with occurrence of blind spots (seen only around day #25). The top panel of Fig. 7 presents a summary of her ranking of 15 of these features on three days of the 41 days of the study: day 1 (the day of the first ABR session), day 25 (a day in the middle in which many features were observed to suffer severe degradation), and day 41 (the last day of log entries, which preceded the second ABR session by 2 days). The lower panel of Fig. 7 shows the peak-by-peak REP score profile for her two REP sessions. Note that although we do not have REP data for the "very bad" day #25, note that the REP profiles reflect very well even the subtle decrement in her overall status comparing day 1 and day 41 (feature-rank sum fell from 67 on day 1 to 59 on day 41, while REP scores changed from 23 late/low, 4 early/high to 27 late/low, 4 early/high). Then, based on these REP-score totals, we placed this individual subject within the original population of 13 MS patients (Fig. 8); her two sets of REP scores predicted that her disease status resembled that of subjects VS and RA. The attending neurologist for the first 13 patients agreed that JS's case history and description of current symptoms indicated that she would be most similar to his subject VS in terms of overall disease severity.

CONCLUSIONS

These very encouraging results for our initial clinical application of the REP protocol provides a basis for expanding our clinical REP research. For example, we have collected preliminary data illustrating patterns of ABR stability in an addicted smoker which not only change when she goes on and off cigarettes, but are also different from those of her ("non-addicted") husband tested under the same smoking/non-smoking conditions. Her personal history indicates that the REP/ABR test may be helpful for studying hyperactive children, and perhaps diagnostic of which children will be responsive to Ritalin. (We hope to report results of REP/ABR testing with a series of hyperactive children and substance-abusing adults at the spring meeting of ASA.) We have also begun using REP/ABR to study individuals with adrenoleukodystrophy, Alzheimer's Disease, and central auditory disorders, and have plans for exploring the feasibility of using REP/ABR for prognosis in comatose adults as well as children at risk for Sudden Infant Death Syndrome. At the present, it appears as though the REP strategy may be valuable not only in characterizing individual characteristics of the auditory central nervous system, but may also provide an index of brainstem integrity useful in a wide range of neurological disorders.

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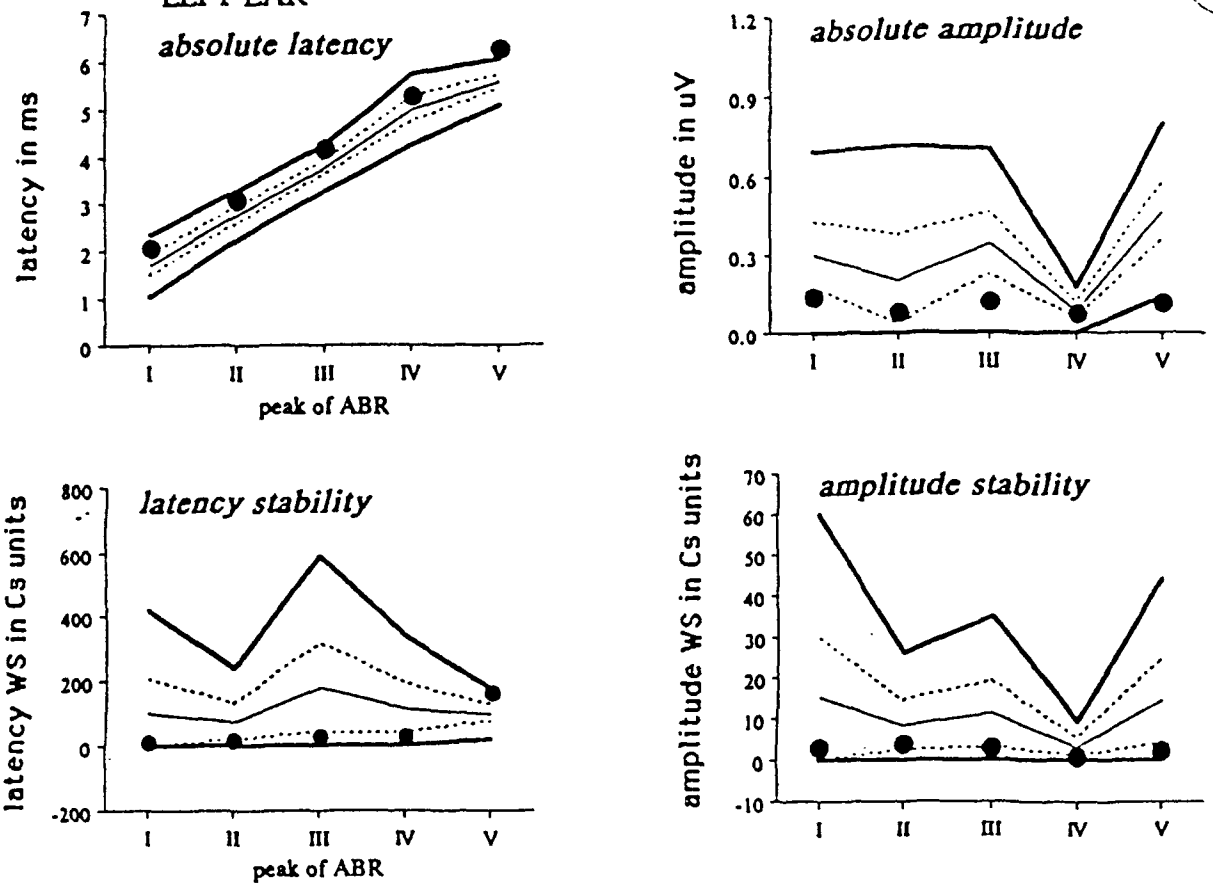


1

2

JU REP score sheet

ear	peak I	peak II	peak III	peak IV	peak V
LEFT	abslat late (>1sd) absamp low (>1sd) latCs low (>1sd)	abslat late (>1sd) latCs low (>1sd)	abslat late (>1sd) absamp low (>1sd) latCs low (>1sd) ampCs low (>1sd)	abslat late (>1sd) absamp low (=1sd) latCs low (>1sd) ampCs low (>1sd)	abslat late (>3sd) absamp low (>3sd) latCs high (=3sd) ampCs low (>1sd)
RIGHT	latCs low (=3sd)	abslat late (>3sd) absamp low (>1sd) ampCs low (>1sd)	abslat late (=1sd) absamp low (=1sd) latCs low (>1sd) ampCs low (>1sd)	abslat late (>1sd)	abslat late (>1sd) absamp low (>1sd) ampCs low (>1sd)
BINAURAL	abslat late (>1sd) absamp low (>1sd) latCs low (>1sd) ampCs low (>1sd)	abslat late (>1sd) latCs low (=1sd) ampCs low (>1sd)	abslat late (>1sd) absamp low (>1sd)	abslat late (=1sd)	abslat late (>3sd) absamp low (>1sd) latCs low (=1sd) ampCs low (>1sd)
BIN =2 (new)			latCs low (<1sd)		

7L
1H
3L
10L, 1H

6L	6L	Overall	38
0			2
0			4
			44

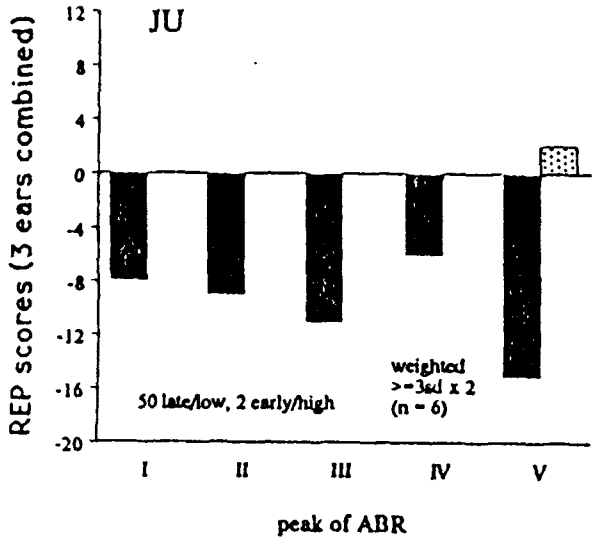
11L	11L	Binaural	14
0			0
0			1
			15

7L	8L	Right	10
0			1
1L			1
			12

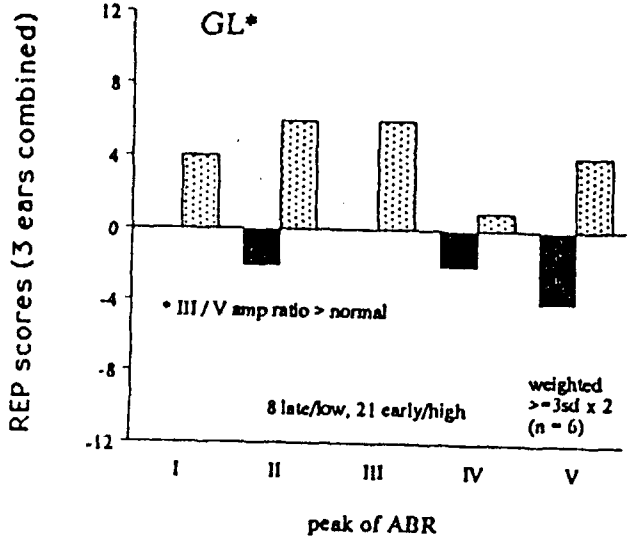
TOTALS				
=> 1sd	7L	8L	Left	14
= 3sd	1L			1
> 3sd	0			2
		GRAND TOTAL	REP Totals	17
			=> 1sd	
			= 3sd	
			> 3sd	

1wld =>3sd x2 = 50L, 2H

A



B



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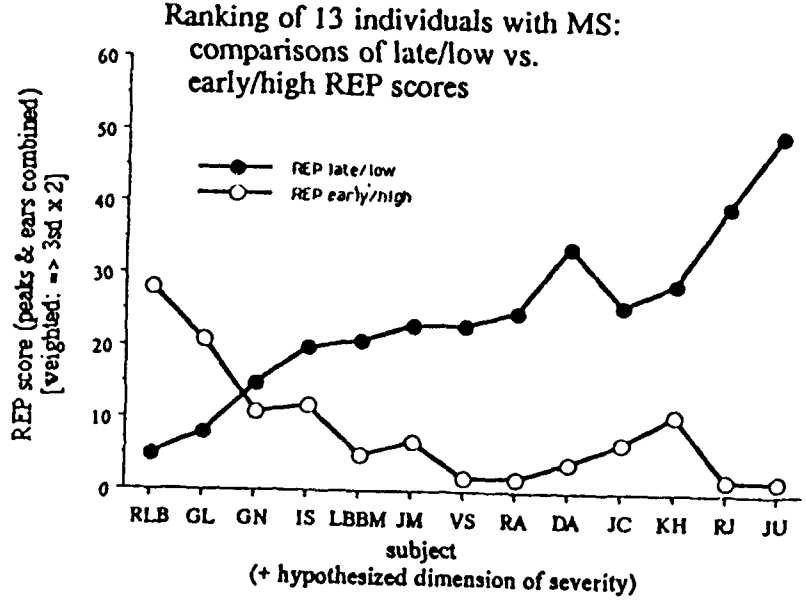


5

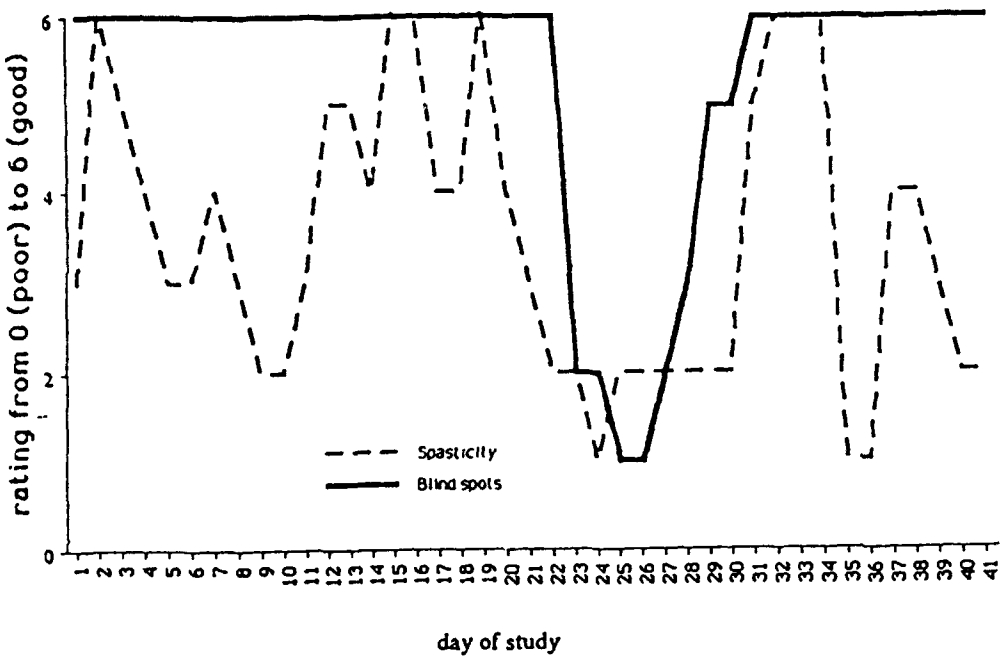
REPs ranking: clinical ranking:

mild

RLB	RLB	
GL	GL	
GN	GN	< LBBM
IS	IS	
LBBM		< VS
JM	JM	
VS		
RA		
DA	DA	
JC	JC	< RA
KH	KH	
RJ	RJ	
JU	JU	

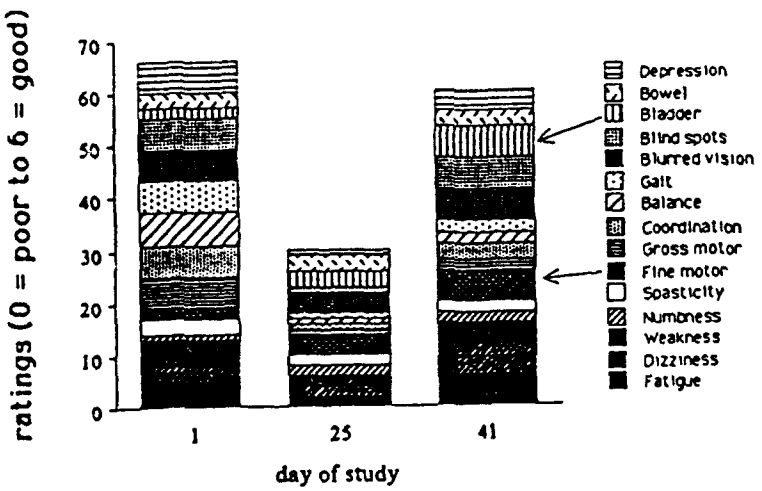
(6)

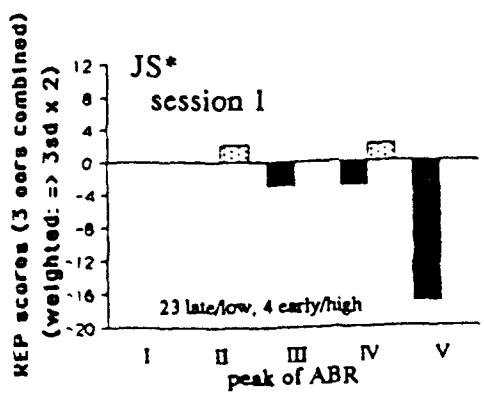
J S daily log:
Extremes of variability -- spasticity vs. blind spots

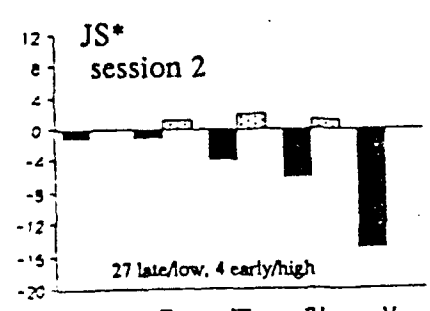


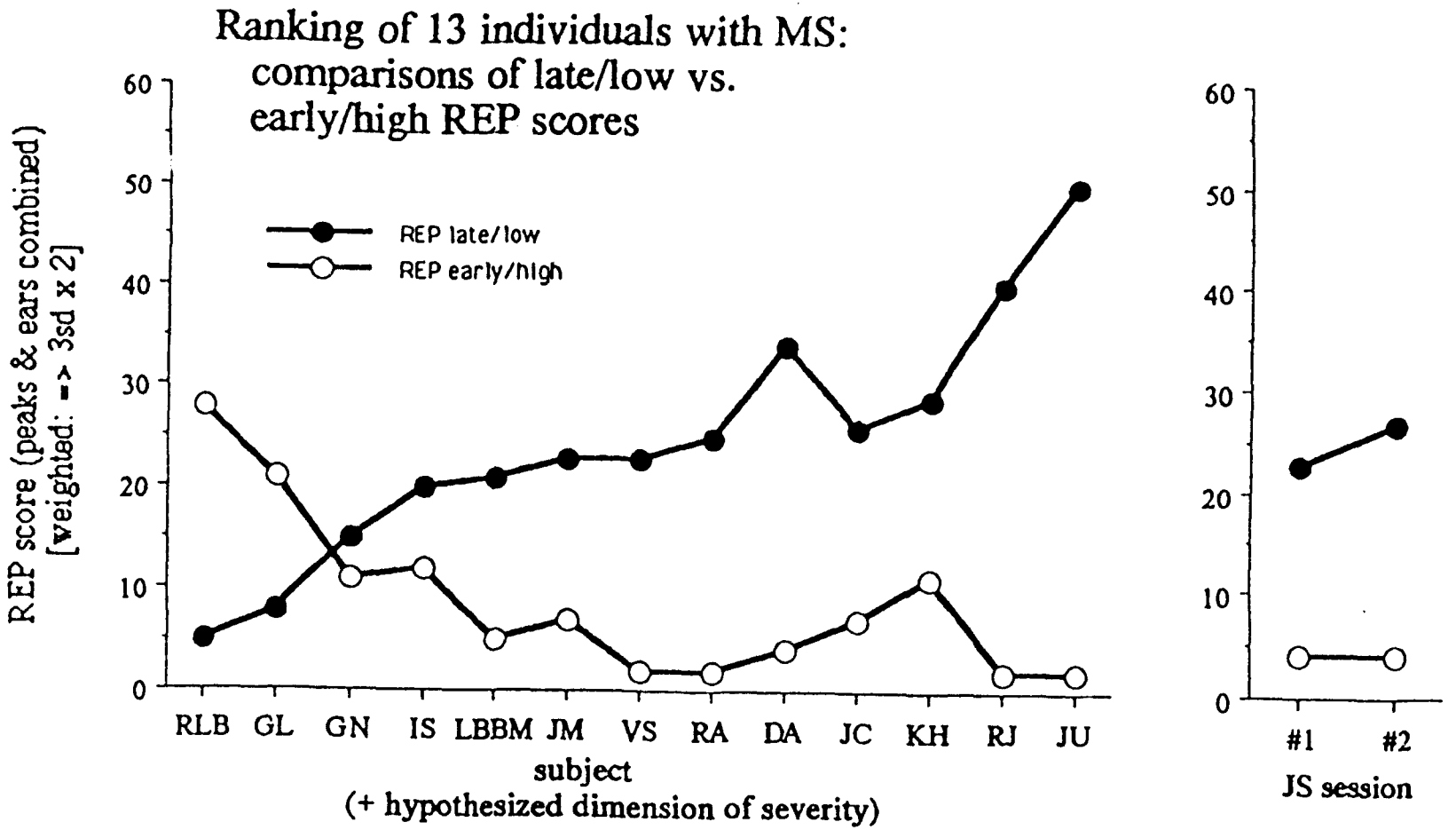
(7)

JS daily log summary: 15 measures








Ranking of 13 individuals with MS:
comparisons of late/low vs.
early/high REP scores
REP score (peaks & ears combined)
[weighted: => 3sd x 2]
REP late/low
REP early/high
60
50
40
30
20
10
0
RLB GL GN IS LBBM JM VS RA DA JC KH RJ JU
subject
(+ hypothesized dimension of severity)
#1 #2
JS session

Comparisons of between- and within-subject variability in repeated-measures auditory brainstem responses (ABRs) in 10-12-year-old children. Robert F. Oyler and Judith L. Lauter (Dept. of Speech and Hearing Sciences, University of Arizona, Tucson, AZ 85721). Presented to Acoustical Society of America, St. Louis MO, November 1989.

ABSTRACT

In reports to this Society, and publications [J. L. Lauter and R. L. Loomis, Scand. Audiol. 15, 167-172 (1986); Scand. Audiol. 17, 87-92 (1988)], results of repeated-measures ABR testing in young adults have been described, indicating that the variability of peak parameters, such as latency and amplitude, provides information that absolute values of these parameters do not: contrasts in between- versus within-subject consistency, and by ear of stimulation. Nine 10-12-year-old boys were tested in four biweekly sessions, with five ABR waveforms collected in each session for monaural right, monaural left, and binaural clicks. Relative variability measures of ABR latencies reveal adultlike patterns based on nonadult values: (1) contrast in between- versus within-subject consistency; (2) peak differences; and (3) ear differences. There are also differences in within- versus between-session consistency. Preliminary comparisons with results of similar testing in 5-7-year-old children [J. M. Lord-Maes and J. L. Lauter, J. Acoust. Soc. Amer. 85, S38 (1989)] and adults suggest that ABR variability may be sensitive to auditory-system developmental changes that continue long after ABR absolute peak latencies have achieved adult values.

INTRODUCTION

Over the past few years, we have reported findings regarding the relative variability of ABR peak parameters, based on within-subjects repeated-measures testing (see references).

Very simply, the design involves examining each subject in several sessions. For example, the first slide (Fig. 1), shows that Subject CR was tested in a schedule of 8 weekly sessions with each session scheduled at the same time of day on the same day of the week. By testing a number of subjects in this way, we can not only obtain the conventional waveform measures such as peak latency and amplitude, but we can also calculate mean and standard deviation of such parameters. These means and standard deviations can be calculated either across subjects, to determine the degree of consistency among the members of a group, or within subjects, to determine the stability of each individual's responses over time. Both of these measures are an expression of the degree of individual differences within a group of subjects.

In our previous work with young adults (reports cited above), we have found that this type of testing can reveal characteristics of ABRs that are invisible if just the usual, absolute values are considered. For example, in the next slide (Fig. 2), mean latency of each of five ABR peaks observed in a group of seven young adults is plotted in the left panel. As is well known, the only variable affecting these curves is peak: latency increases for later peaks. There are no differences due to ear of stimulation--the functions are virtually the same for right-ear,

left-ear, and binaural conditions--or whether calculations are made between or within subjects--that is, obtaining an average over subjects for each session, then averaging over sessions, or obtaining an average over sessions for each subject, then averaging over subjects.

However, as shown in the right panel, if we not only measure latency mean but also latency standard deviation, calculated both between- and within-subjects as I have just described, and then plot the derived ratios of mean and standard deviation, we see a very different type of graph, where the values of the ratio are shown to be sensitive to all three variables we've mentioned--there are statistically significant differences here distinguishing the effects of peak, ear, and within-subjects (WS) vs. between-subjects (BS) comparisons. On this type of graph, higher values mean greater stability. Thus, for example, consistency within individuals (the "Within subjects" curves) is generally greater than between individuals (the "Between subjects" curves). The between-subjects curves indicates the degree of individual difference among the members of this group, and the within-subjects values indicate how consistent individuals are when compared with themselves over time. Statistically, the differences break down as: binaural responses more stable than either monaural, peaks II through V more stable than peak I, and within-subject consistency greater than between-subject consistency.

If we calculate the same index for individual subjects, computing each person's latency mean and standard deviation over repeated sessions, we can see individual differences. The next slide (Fig. 3) shows examples of these differences, with each subject's mean latencies on the left, and latency-stability (Cs) profiles for right, left, and binaural stimulation on the right; and the next slide (Fig. 4) illustrates that these profiles for individuals can be replicated from month one to month two of testing (here, profiles for each subject's first four weeks are represented by the open symbols, for the second four weeks by the filled symbols). We have concluded from these types of findings that such descriptions of ABR stability may provide "fingerprint" characteristics of individual auditory nervous systems. As a side note, though we've presented only results for latency stability here, similar patterns occur for amplitude stability, as well.

Last spring, we reported to this Society an extension of this type of testing to a group of 5-7-year-old children (Lord-Maes & Lauter, 1989). The next slide (Fig. 5) summarizes those results. While, as the literature would predict, the children's mean latencies (left panel) are identical to adult values, the latency-stability measure (right panel) show them to be unlike adults: 1) the WS values are significantly lower for all peaks except peak I than for adults; and 2) there are no differences due to ear in the WS curves. The way in which these children do resemble adults in terms of latency stability is that within-subject consistency is significantly greater than between-subject consistency--that is, just as for adults, according to this measure, these children are more like themselves than they are like each other. The children also show individual differences in latency stability, which may replicate over the two months of testing.

Today we will describe results of a similar repeated-measures ABR test series in a

group of 10-12-year-old children. We were to curious to see whether, according to our latency-stability measure, children at this age resembled the 5-7-year-olds, the adults, or whether they would be intermediate between younger children on the one hand, and adults on the other.

METHODS

Nine 10-12-year-old boys were recruited for a series of four biweekly test sessions. In each test session, ABR waveforms for right-ear, left-ear, and binaural stimulation were collected, using standard clinical test procedures. Details are shown in the next slide (Fig. 5). Analysis consisted of identifying the first five vertex-positive peaks in each waveform, and measuring the latency of each peak. Then calculations of latency stability were made, as described earlier, computing the ratio of latency mean to standard deviation, both for: 1) between-subject comparisons to describe consistency of each group; and 2) within-subject comparisons to describe consistency within individuals.

RESULTS

The next slide (Fig. 6) summarizes the results. On the left, mean latency values are plotted--as for the younger children and the adults, there are no differences due either to ear or to within-subjects vs. between-subjects averaging.

Latency stability is shown on the right. Statistical tests indicate that within-subject stability is greater than between-subject at all peaks except peak IV, and that there are peak differences in the within-subject values but not for between-subjects.

There is also a significant main effect for peak, accounted for by latency stability at peaks III and V being significantly greater than for the other peaks. The main effect for group comparison indicates that overall, within-subject stability is significantly higher than between-subject. Unlike the adults, there are no differences in these values that distinguish among ears.

The last slide (Fig. 7) compares latency-stability plots for all three age groups. Statistical comparisons of values representing all groups indicates that in terms of within-subject consistency, the 10-12-year-olds are in fact intermediate betwen the other two groups: 1) WS latency stability at peaks II and IV is similar in the two groups of children, and lower in both groups than in adults; but 2) WS latency stability at peaks III and V is similar in the older children and adults, and greater in both groups than in the younger children.

Admittedly, these results are very preliminary. Further testing with larger groups of subjects, representing more ages, must be done before we can understand their implications. However, all of our findings to date suggest that variability measures such as these promise to give us new information regarding the characteristics of individual sensory nervous systems, and may thus prove useful for understanding both normal and disordered processing.

Certainly one preliminary conclusion regarding the results we have shown today, is that ABR peak latency variability, based on this type of repeated-measures within-subjects testing, may reveal developmental changes which persist long after the absolute latencies of ABR peaks reach their adult values.

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[Fig 1 omitted]

adults (Grp I) (7 Ss, 8 sessions)

Fig. 2

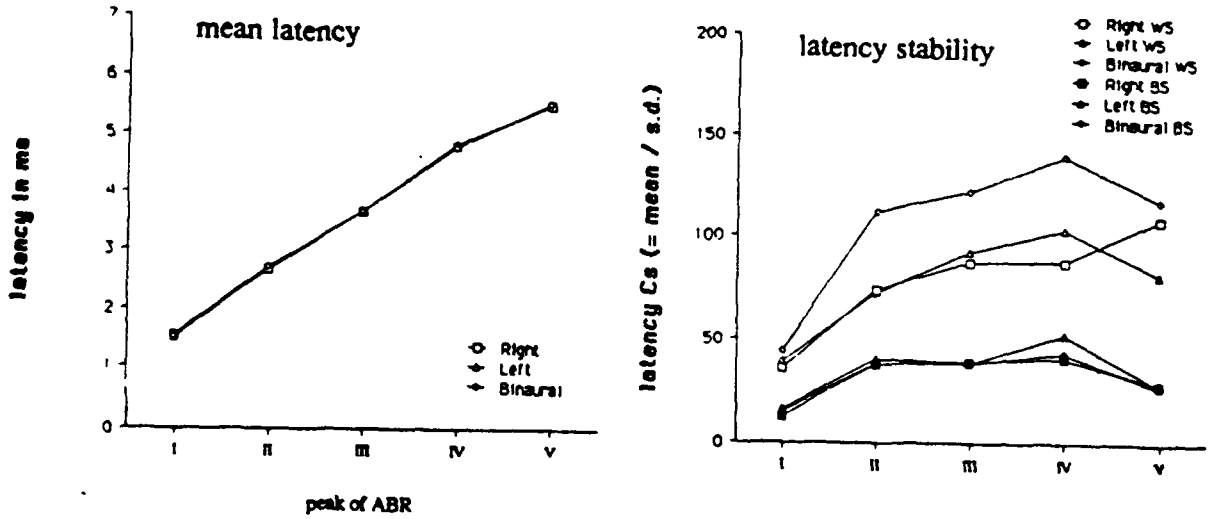


Fig. 3

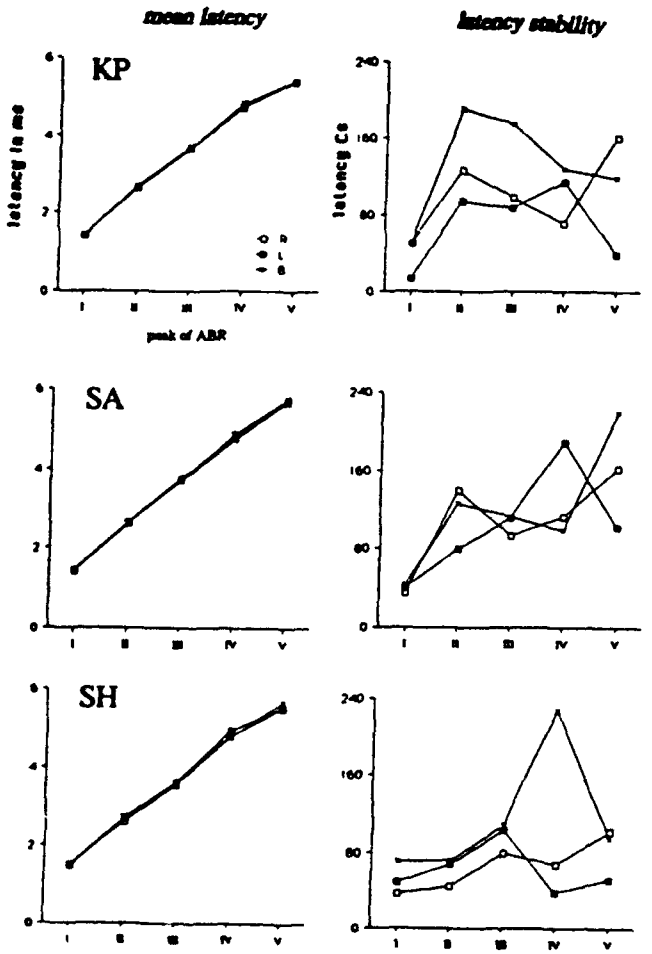


Fig. 4

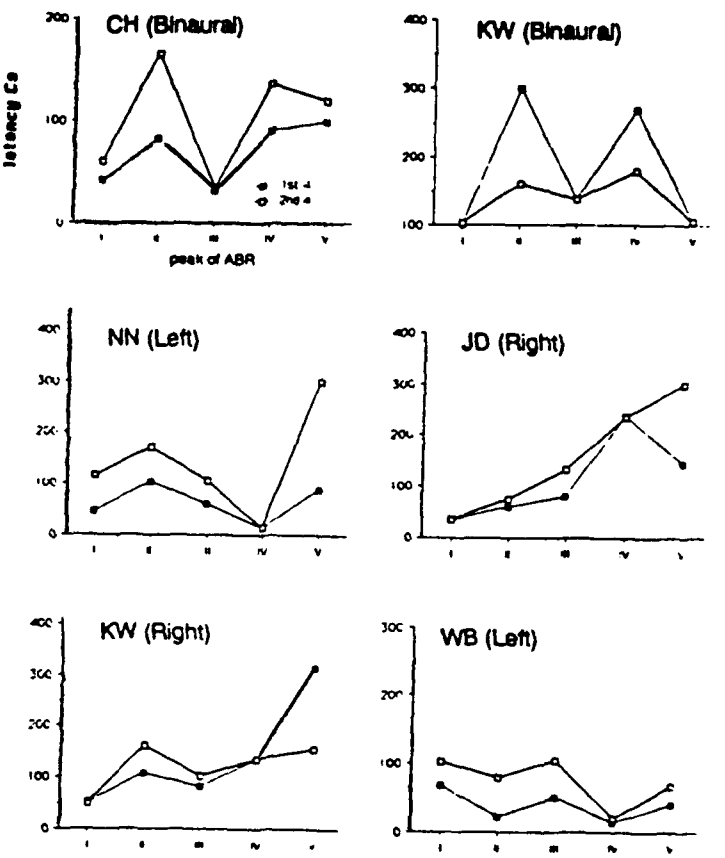


Fig. 5

5-7 years (7 Ss, 8 sessions)

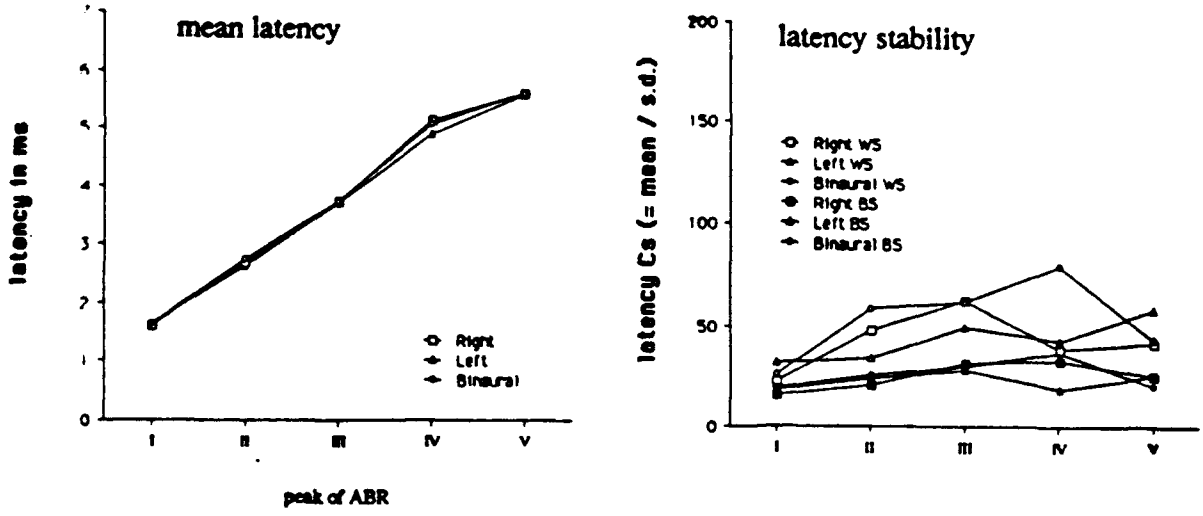


Fig. 6

10-12 years (9 Ss, 4 sessions)

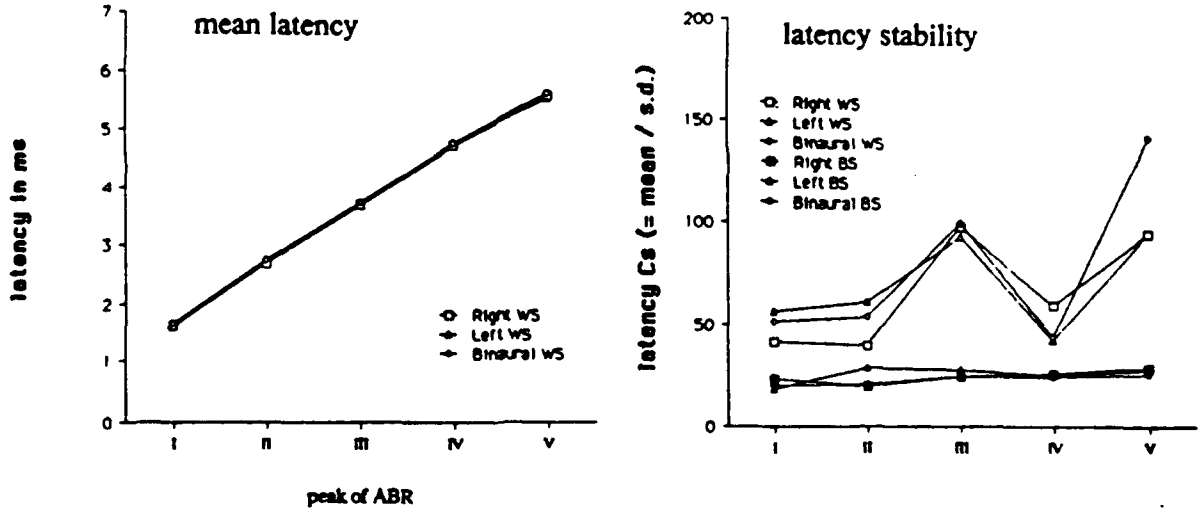
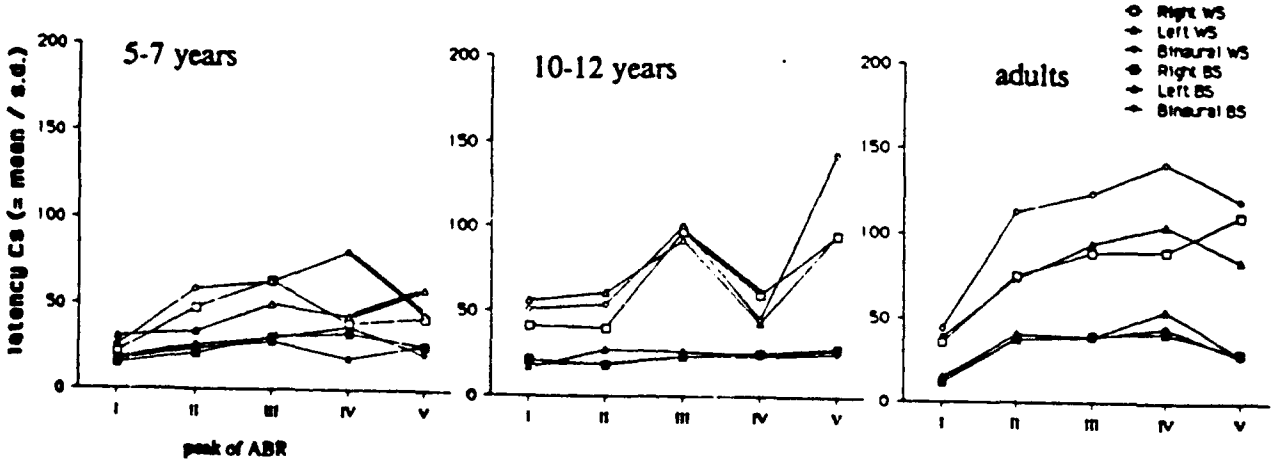


Fig. 7



Central auditory dysfunction: qEEG and MRI correlates of individual differences in ear advantages and REP/ABR results. Judith L. Lauter (John Keys Speech & Hearing Center, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73190). Presented to Acoustical Society of America, November 1991, Houston TX. Abstract: J Acoust Soc Amer 90: 2292.

ABSTRACT

A new test battery for central-auditory diagnostics, supplementing standard audiometry with MacCAD (a Macintosh-based program for central auditory diagnostics), and the ABR version of our repeated-evoked potentials (REPs) protocol, was described to the spring 1991 meeting of this Society (Lauter 1991 a,b). As reported then, preliminary results distinguished among a variety of patients, with some details predictive of individual patterns of supra-brainstem involvement. Subsequent testing of the same subjects using quantitative EEG together with MRI provides initial support for these predictions. For example, in one subject originally diagnosed as "central auditory," previous findings such as "polar-opposite" ear advantages and "release signs" in ABR stability profiles, were accompanied by qEEG characteristics such as reduced beta power over auditory cortex bilaterally, and diminished interhemispheric coherence. Similar findings in other subjects suggest that by exploiting the sensitivity of repeated-measures test designs to individual characteristics, it may be possible to generate more detailed physiological and behavioral profiles of central auditory function.

INTRODUCTION

Long-standing frustration with understanding the variety of disorders resulting from putative malfunction within the human central auditory nervous system is accounted for at least in part by: 1) the lack of sensitivity in currently-available tests for evaluating behavioral features of either normal or disordered "central function," and 2) lack of noninvasive tools for examining brain structure and processing. The first issue may be addressed by careful design of new behavioral tests for central function, based on pyschophysical principles of manipulations in stimulus and task complexity (Lauter 1984a, 1990a), and the second by selective use of several available ways to quantify individual characteristics in brain anatomy and physiology, such as Magnetic Resonance Imaging (MRI), Repeated Evoked Potentials (REPs), quantitative EEG (qEEG, also referred to as "BEAM" and "Brain Mapping"), Magnetoencephalography (MEG), and Positron Emission Tomography (PET) (Lauter in Press, a, b; in Preparation). While future applications of all such techniques may provide dramatically new insights into human auditory function, for practical clinical applications in the short term, early efforts along these lines must make use of readily-available and relatively inexpensive technologies.

The MacCAD program for Central Auditory Diagnostics on the Macintosh requires only a Macintosh SE/30 computer with no additional hardware. The program makes use of principles generated in our studies of central auditory function in normal young-adult subjects (Lauter 1982, 1983, 1984b), including collecting ear advantages (EAs) on each subject for at least two sets of

sounds (e.g., synthetic stop-CV syllables vs. "slow" three-tone patterns), and the use of graduated-difficulty versions of each sound set such that ear advantages are based on scores representing mid-range performance (i.e., neither ceiling nor floor) in at least one ear. The MacCAD program realizes these and other principles in a highly interactive format which involves the client as an active participant in testing, and shows good subject acceptability, particularly in individuals who have little or no familiarity with computers.

Minor modifications in standard clinical procedures for Auditory Brainstem Responses (ABRs), consisting primarily of using a repeated-measures design so that the same test is run several times (Repeated Evoked Potentials: REPs), has proven to provide striking increases in sensitivity of this widely available type of physiological test, both for specifying individual characteristics as well as for documenting the effects of both peripheral and central pathology (Lauter and Loomis 1986, 1988; Lauter and Karzon 1990a,b,c; Lauter and Lord-Maes 1990a,b; Lauter and Oyler in Press). A simple scoring procedure has been developed for this type of testing which compares individual data against a normal database according to a variety of measures, including absolute values of latency and amplitude as well as indices of of latency and amplitude stability.

PREVIOUS FINDINGS

Results from MacCAD and REPs/ABR testing of two "central auditory" individuals were reported to this Society in the spring of 1991 (Lauter 1991b) (Figs. 1 and 2). As described at that time, the findings for subject MAB (Fig. 1) included: 1) normal performance on a standard battery of audiometric tests, including a conventional "central test," 2) a "drop-out" in the ear-by-sound EA matrix as tested with MacCAD, in which performance level in both ears on both sound sets was comparable with the single exception of the condition of right-ear attention to the synthetic stop CVs; and 3) indication of an abnormality at ABR peak IV in the response to right-ear clicks, as expressed in his "REP score profiles" (lower panel of Fig. 1).

The nature of the peak-IV abnormality, in that it consisted of a deviation from normal in terms of the "early/high" score category rather than in "late/low" scores, suggested a cortical abnormality involving the contralateral, or left hemisphere. This observation seemed to agree with the MacCAD results, which suggested a failure involving processing related to processing of syllables via right-ear input. The resulting hypothesis was that MAB's difficulty involved a failure in processing localized to auditory-cortical regions in the left hemisphere.

For subject SHB (Fig. 2), the results obtained with MacCAD comprised "polar opposite" EAs contributed to by near-ceiling performance in the "preferred ear" and near-floor performance in the opposite ear, with a <u>complementary pattern</u> for the two sound sets. These findings suggested a "disconnection" relation between left- and right-hemisphere auditory cortex. The possibility of problems involving either connections between the two sides, or perhaps lateralized to both sides, was borne out by the REP/ABR results, which indicated early/high type abnormalities in the ABR REP-score profiles in <u>both</u> monaural conditions.

METHODS

In order to explore the cortical involvement in these two subjects, each was scheduled for a MRI brain scan, to support measurements of anatomical asymmetries in auditory cortex (cf. (Plante et al. 1989; Lauter and Plante in preparation), and tested in a qEEG session using procedures reported previously (Lauter 1988; in Press, c), focusing on measurements of physiological asymmetries observed over auditory cortex during resting as well as auditory-activation conditions.

MRI testing and analysis. Test parameters and analysis procedures for MRI were identical to those developed by Plante for the study of auditory anatomical asymmetries (Plante et al. 1989). Films of twenty five-mm contiguous axial MRI slices taken on a Toshiba 0.5 T scanner were measured with a Jandel Java image-processing system to obtain: 1) values for whole-hemisphere volume, contrasting left vs. right, and 2) values for periSylvian cortical volume, left vs. right. Left/right differences in each measure were expressed as a difference/sum ratio:

$$\frac{\text{(L-side volume) - (R-side volume)}}{\text{(L-side volume) + (R-side volume)}} \times 1000$$

Thus for each individual, two such ratios were obtained: one expressing the direction and magnitude of whole-hemisphere volume asymmetry, and another expressing direction and magnitude of periSylvian cortical volume asymmetry.

qEEG testing and analysis. Each subject was also scheduled for a qEEG session similar to those reported previously (Lauter 1988; in Press, c). An electrode cap provided simultaneous recording via a Cadwell Spectrum 32 Neurometrics system from multiple locations across the scalp during 11 5-min test conditions, according to the following schedule (note that all activation conditions duplicated test conditions with which the subject had become familiar during prior behavioral testing with MacCAD):

1) resting
2) monaural synthetic CVs (same as those used in MacCAD) presented to the left ear
3) monaural-right CVs
4) dichotic CVs, attention to R ear
5) dichotic CVs, attention to L ear
6) resting
7) monaural three-tone patterns (same as used in MacCAD) to right ear
8) monaural-left tone patterns
9) dichotic tone patterns, attention to L ear
10) dichotic tone patterns, attention to R ear
11) resting

Measurements provided by the Cadwell system for the qEEG data under each condition included values for each of four qEEG bandwidths describing activity over electrode locations T3 and T4 (auditory cortex) according to: absolute power, relative power, power asymmetry, and coherence.

RESULTS

SHB. For this subject, two findings derived from the MRI and qEEG measures may be related to her functional "disconnection" syndrome. First, in contrast to most of the other normal subjects we have tested previously, she had a striking degree of anatomical symmetry in both her whole-hemisphere volume and perisylvian volume measures. This is illustrated in Fig. 3, where results from 7 normal adults are presented for comparison with SHB's data. Note that, in contrast to the normal females, SHB has virtually no whole-hemisphere volume asymmetry, and her perisylvian asymmetry is also much smaller than that seen in any of the normal subjects. It is possible that a lack of normal asymmetry is associated with some abnormality in the quality of communication between the hemispheres, which could account for the "polar opposite" ear advantages observed earlier for this subject.

The qEEG findings for SHB revealed two details of interest. First, there was a very small resting asymmetry in beta-band power comparing T3 vs. T4, less than 5% difference, which was thus in keeping with the MRI perisylvian asymmetry, i.e., virtually no asymmetry comparing left vs. right auditory cortical areas. Figure 4 illustrates this general lack of asymmetry via a comparison of the fluctuation in T3/T4 beta-band power during three resting conditions for SHB (middle) and two normal subjects, one with a marked left-hemisphere advantage (LHA) in perisylvian cortical volume (ES), and one with a marked perisylvian RHA (JL). Note that overall, SHB's data show very small differences between the two sides, particularly when compared to the two normal subjects. However note also that the agreement between the direction/magnitude of perisylvian vs. T3/4 asymmetry shown in all three subjects is representative of a phenomenon which we have consistently observed in normal individuals (Lauter and Plante in preparation).

The most strikingly abnormal characteristic of SHB's qEEG findings was expressed in a measure which may be even more directly related to the functional "disconnection" observation, namely, inter-hemispheric coherence. Figure 5 compares the degree of coherence seen in the four EEG bands below 20 Hz, for a group of normal subjects vs. that seen in SHB's data. The high degree of coherence typically found in the normals in the lowest-frequency band ("delta") was lacking for SHB: her delta coherence was as low, if not lower than that observed for the other bands, both in her results as well as in normals. It is possible that this lack of low-frequency coherence (more than two standard deviations below the mean value for the group of normals) is a physiological sign of dysfunctional "cross-talk" between the two hemispheres, which could possibly be related to the apparent lack of cross-pathway interference in SHB's dichotic results.

MAB. The MRI results for MAB (Fig. 6) showed a pattern of anatomical asymmetries which was much more normal than for SHB: namely, with marked asymmetries in both whole-hemisphere and well as perisylvian volume, both favoring the left hemisphere. Note, for example, the similarity between the pattern of MAB's MRI asymmetries and those shown for normal subject ES, and the clear difference contrasting these two with SHB.

However, this perisylvian cortex anatomical asymmetry is not reflected in MAB's physiological asymmetry in beta power measured over T3/4. Figure 7 contrasts the lack of asymmetry with

patterns of T3/4 beta asymmetry seen in the two normal subjects from before, ES and JLL. Like MAB, each of these two normal subjects had large periSylvian anatomical asymmetries (values given below the names) which were reflected in similarly large qEEG asymmetries (shown in the plotted data), which matched the MRI asymmetries in both magnitude and direction. However, MAB's data are remarkable in that his similarly large MRI asymmetry co-occurs with a consistent lack of resting qEEG asymmetry, contributed to by an "appropriately" low level of beta activity on the non-anatomically-dominant side combined with an disproportionately low level of beta activity on the anatomically-dominant side. This failure of the anatomically-dominant area to be physiologically dominant may be a direct sign of the underlying problem which expressed itself in the "drop-out" score of MAB's results on the dichotic listening test, where the only truly low score was received when he had to attend to syllables (presumably a "left-hemisphere sound" in this pRfR subject) in his right ear. This "physiological failure" in left-hemisphere auditory cortex may also account for the "early/high" REP score abnormality seen in MAB's right ear ABR, suggesting that diminished activity in the left auditory cortex is associated with a contralateral "release" sign in the ABR.

CONCLUSIONS

These admittedly preliminary results indicate that the concept of testing individuals diagnosed as "central auditory" with a variety of tests for quantifying auditory CNS structure and function is a viable one. They also suggest that if procedures are selected carefully with an eye to achieving results which can be directly related to one another, we may expect new insights into the mechanisms underlying such complaints.

This test-battery approach, in which several noninvasive technologies are combined to study the same or closely related experimental questions in a within-subject, repeated-measures design, is the strategy behind the Coordinated Noninvasive Studies (CNS) Project, which has been under way in our laboratory for several years (Lauter 1988, 1989, 1990b; 1991c,d; Lauter and Plante 1989; in preparation). The focus in this Project to date has been on asymmetries in human auditory processing in normal subjects, and the results reported here represent an initial clinical application of the procedures and methods developed during the early years of the Project (cf. Fig 10 for a sample comparison of "CNS profiles" contrasting normal subject ES, and our two "central" subjects, MAB and SHB). The CNS strategy is clearly applicable to a number of issues involving structure and function of the human brain, and it is hoped that as we continue to develop and streamline our methods for practical clinical applications, additional insights into human brain development and function will be forthcoming, not only in frankly neurological populations but also in others in which neurogenic components of dysfunctional states are poorly defined or only suspected.

ACKNOWLEDGEMENTS: We would like to acknowledge several individuals' help with data collection: Colette Coe (audiometry), Nancy Solomon (MacCAD), and Jan Lord-Maes (REP/ABRs). Special thanks are due to Elena Plante for overseeing the MRI data collection, and applying her insightful and meticulous procedures to the analysis of the MRI anatomical aysmmetries.

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(1)

Subject: MAB ♂
Age: 27
Sidedness: pRfR: no twins

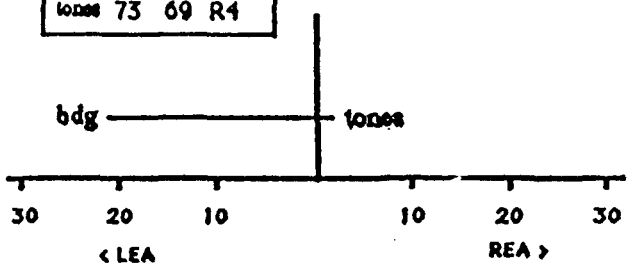
Audiometry:

1. Pure-tone results normal bilaterally.
2. Word recognition ability excellent bilaterally.
3. Normal impedance findings and normal acoustic reflexes bilaterally.

SSI: 100% Right, 87% Left

MacCAD:

scores:	R	L	EA
syll	31	56	L25
tones	73	69	R4



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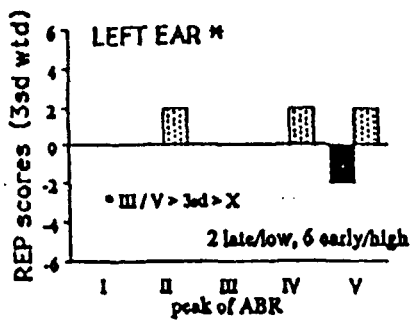
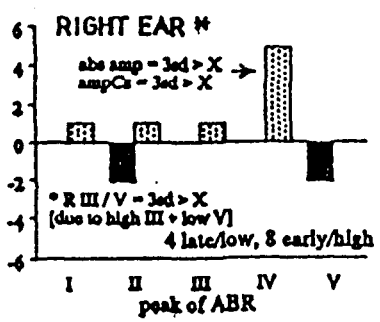




(2)

Subject: SHB ♀
Age: 40
Sidedness: pRfR: no twins

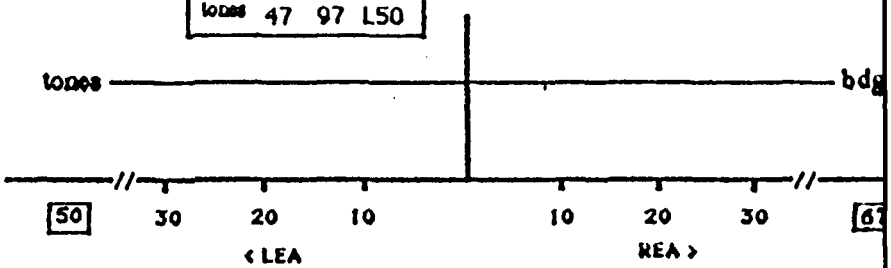
Audiometry:

1. Pure tone audiometry normal for both ears, 250 - 8kHz.
2. Word recognition ability excellent bilaterally.
3. Impedance and reflexes normal in both ears.

SSI: 100% Right, 87% Left

MacCAD:

scores:	R	L	EA
syll	89	22	R67
tones	47	97	L50



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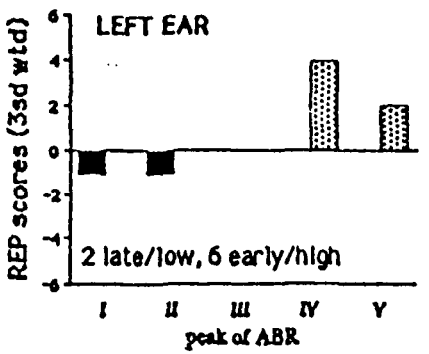
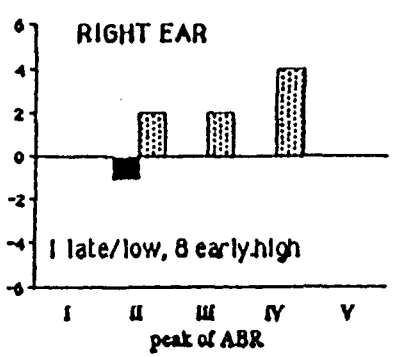
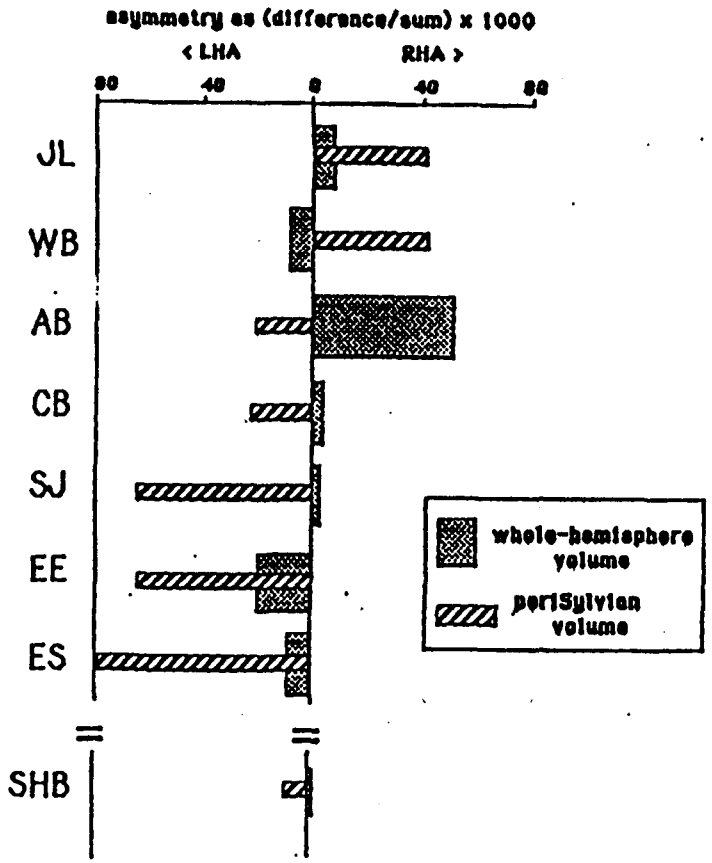




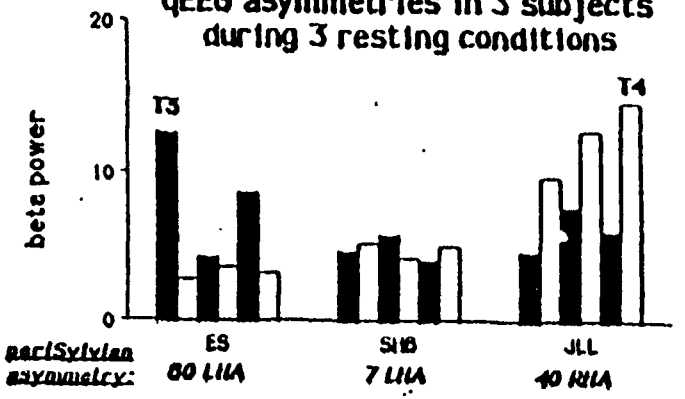
(3)

MRI asymmetries: 7 normal females + 1 CAPD female



(4)

qEEG asymmetries in 3 subjects during 3 resting conditions



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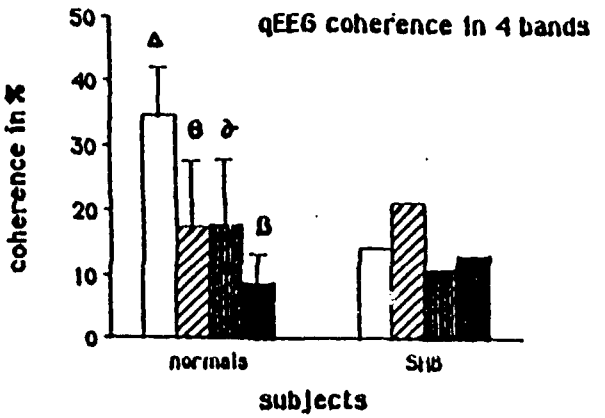
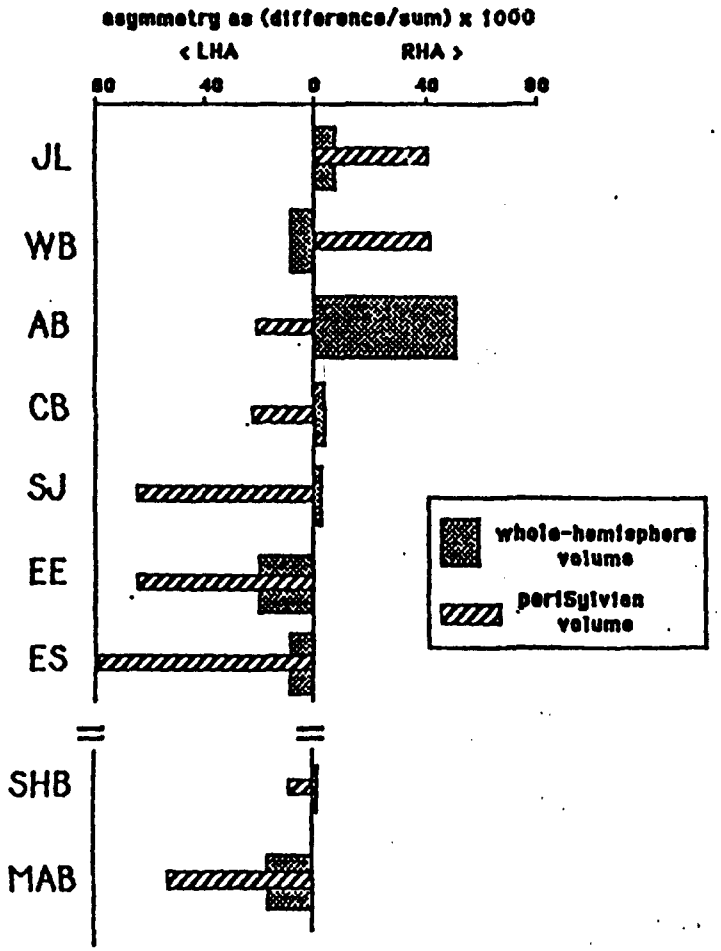
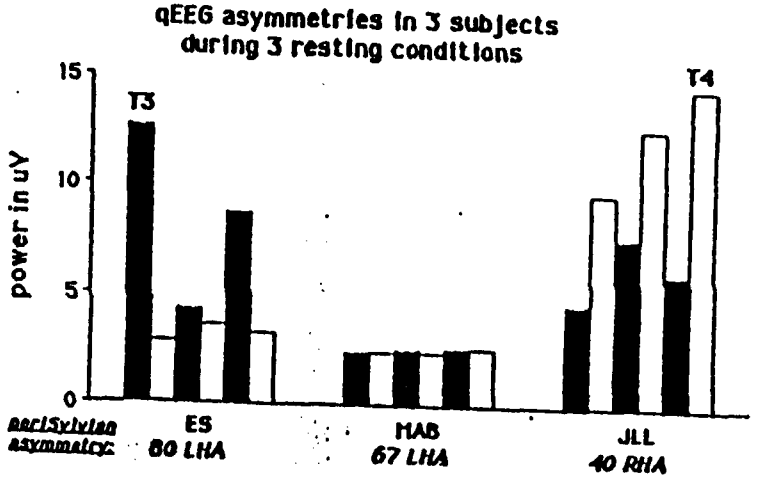


(6)

MRI asymmetries: 7 normal females
+ 1 CAPD female
+ 1 CAPD male

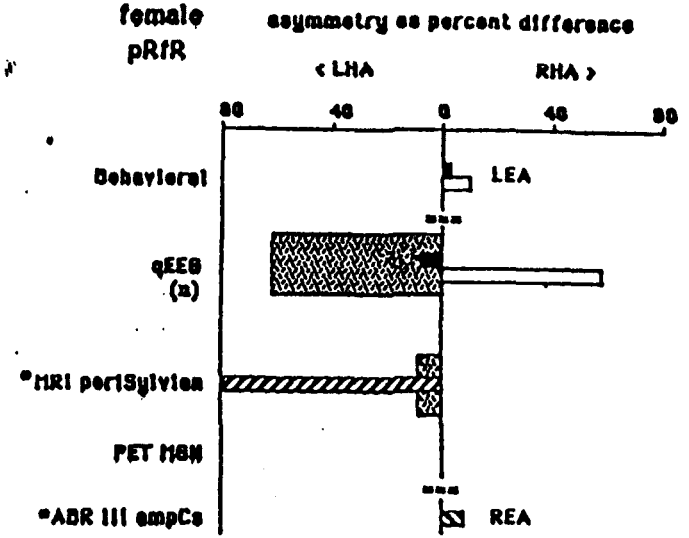


(7)



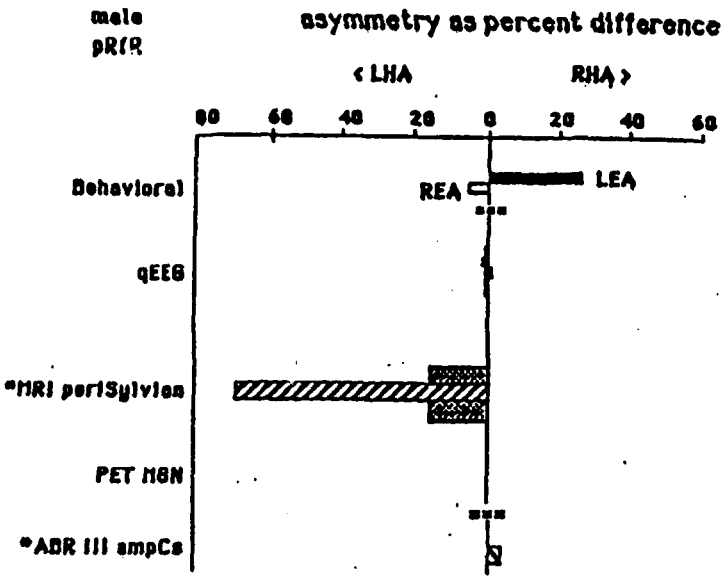
ES

female
pRfR



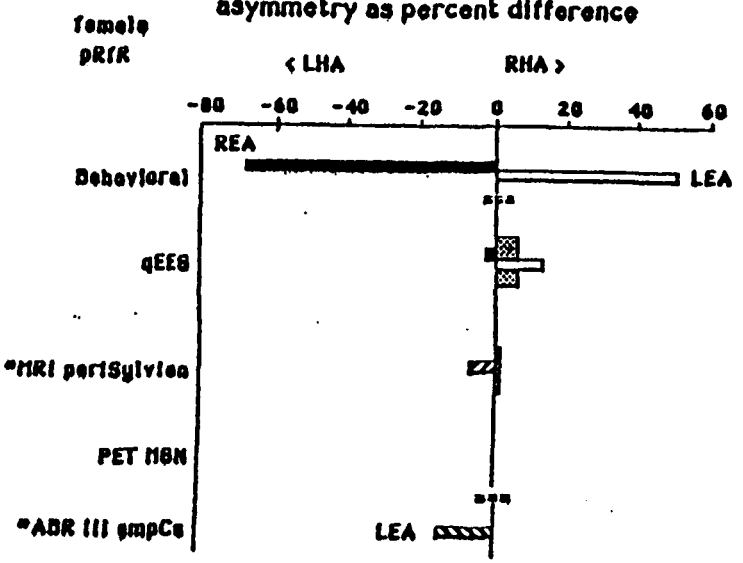
MAB

male
pRfR



SHB

female
pRfR



Appendix E
Related activities II: MacCAD software development

Lauter, J.L., J.M. Lord-Maes, N. Solomon, C. Coe (1991) "MacCAD and REP/ABRs: A new test battery for central auditory dysfunction," presented to Acoustical Society of America, Baltimore MD. Abstract: J Acoust Soc Amer 89: 1975.

Lauter, J.L., J.M. Lord-Maes (1991) "MacCAD and REP/ABRs: A new test battery for central auditory dysfunction," presented to Acoustical Society of America, Baltimore MD. Abstract: J Acoust Soc Amer 89: 1975.

MacCAD, a new Macintosh-based Hypercard program for central auditory diagnostics: description and preliminary findings. *Judith L. Lauter, Nancy Solomon, and Colette Coe (Dept. of Speech and Hearing Sciences, University of Arizona, Tucson, AZ 85721). [Abstract: J Acoust Soc Amer (1991) 89: 1975]

ABSTRACT

Although most components of the classical auditory system lie between the periphery and association cortex, our information about auditory disorders is limited primarily to those extremes. This ignorance is due to the fact that until recently, appropriately sensitive methodologies, both in terms of test design as well as modes for noninvasive brain monitoring, have not been readily available in the clinic. MacCAD is an attempt to address the first of these issues; a companion paper will report on results combining MacCAD with noninvasive physiological testing (Repeated Evoked Potentials [REPs]). MacCAD brings features of basic-research test design into the clinic, including: ease of use by both tester and client, monaural and dichotic modes for a variety of speech and nonspeech sounds, expansion capability for additional sounds, graduated difficulty for each sound set, client control of test pacing, automatic stimulus/response recording, trial-by-trial feedback, and analysis options including trial-by-trial monitoring, confusion matrices, and percent-correct for individual sounds and complete sets. Initial field testing with populations predicted to have damage between periphery and language cortex, including adults with central auditory dysfunction, multiple sclerosis, Parkinson's Disease, and presbyacusis, indicates that MacCAD's unique features may render it sensitive to individual characteristics which, when interpreted in the context of results on other tests such as evoked potentials, may be indicative of auditory dysfunctions which are invisible to standard audiological testing. [Work supported in part by Apple Computer, Inc., Community Affairs, with the American Speech-Language-Hearing Foundation]

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THE OBJECTIVE

MacCAD was designed to address the "problem" of diagnostic testing for central auditory disorders, which in one form or another can affect individuals of all ages, from children with "learning disabilities" to adults with traumatic brain damage to older individuals with "central presbyacusis."

Central auditory testing presents a problem because, as with anything regarding the brain, there are large individual differences in subjects' abilities and characteristic processing strategies, which can, with appropriately sensitive tests, be observed even in normal individuals. Yet conventional tests for this type of hearing make it almost impossible to accommodate and/or characterize such differences among subjects, in spite of the fact that it is very possible that the most interesting facts about individual processing can be revealed only by means of tests which provide such customization.

Our experience studying individual "styles" of central auditory processing in normal young adults (Lauter 1982, 1983, 1984, 1989, In Press) has generated a number of principles for test design which, lacking the "user-friendly" graphic interface of the Macintosh, would be difficult to incorporate into clinical tests. But Hypercard and the Macintosh have made everything easy (Lauter 1990).

DESCRIPTION

MacCAD is thus based on principles of central-auditory test design drawn from our years of basic-research experience with this type of testing (see references). The program makes it possible to "customize" testing to fit age, ability, and dysfunction of the client in ways that conventional central auditory tests based on "Procrustean" approaches to test design (forcing all subjects to take the same version of a test, no matter their abilities), and obsolete supporting technologies (primarily cassette tape, with all its problems of quality control and maintenance) simply cannot do.

The primary relevant limitations of conventional CAD tests (in the typical medium of cassette tape) include: 1) linear mode of access (not random), which requires the clinician to spool through cassette after cassette seeking the desired test; 2) poor expansion capability, since to add new sound sets or entirely new types of tests would just add to the problems of cumbersome access; 3) the form of response most often used (i.e., "repeat what you hear") limits the variety of sounds available almost exclusively to speech sounds, in spite of the fact that nonspeech sounds may provide much more sensitive tests of these disorders; 4) sound quality is poor (important dimensions can be contaminated) and shelf life is limited for the commonly used media such as audio cassette tapes; 5) timing of testing is difficult to adjust -- either the tape runs at its fixed speed (and the

client has to keep up), or the clinician stops it manually (further decreasing shelf life!); and 6) analysis of responses can be done only at a gross level of detail, since scoring is done by hand-- for example, scoring at the word level ("bog" as a WRONG response to "dog") instead of at the sound level (2 sounds were right--the only mistake was confusing "b" vs. "d") can obscure crucial information about an individual client's particular problems, especially regarding the specifics of dysfunction considered within the context of savings.

This table summarizes MacCAD's answers to these problems:

	conventional	***MacCAD***
mode of access	linear	random
expansion capab.	awkward and cumbersome	limited only by storage media limits (hard disk or eventually CD ROM)
response format	"repeat back"	graphic labels --letters or pictures
sound variety	primarily speech	virtually any sound
sound quality	all disadvantages of analog recordings	all advantages of digital recordings
timing flex'b'ty	fixed, or manual stops	client controls the speed
scoring detail	gross level (right/wrong)	any level of detail: specific confusions, etc.

DESIGN FEATURES

The general features of MacCAD include: 1) it consists of a set of HyperCard / HyperTalk stacks, with 2) some HyperSound XCMDs for sound control; 3) MacCAD is designed to be modular, i.e., no stack is larger than 800K (allowing for widest distribution capability); 4) program design provides control over several test parameters for both monaural and dichotic testing with a library of sound sets; 5) all sound sets include "graduated-difficulty" versions to fit the abilities of different clients; the most difficult level included evokes sub-ceiling performance in normal listeners; for example, tone patterns are available in a range of pitch

steps, from whole-tone pitch steps down to eighth-tone step; 6) the program has built-in expansion capability -- user sends 2 stacks back to vendor to get new sounds added to the user's library (returned in turnkey condition); 7) analysis capability includes both on-line and off-line options; eventually may allow for automatic comparisons of an individual client's performance against databases of normals or defined patient populations.

Examples of "graduated difficulty" sound sets are: 1) for synthetic syllables, choices for dichotic presentation include: a)"ba/da/ga" (the targets) vs. "ta" [easier], and b) "ba/da/ga" (the targets) vs. "da & ga" [harder]; 2) for tone patterns, all of which are currently set at 200 ms inter-onset-interval, choices for testing include: a) whole-tone pitch steps between notes [easiest], b) half-tone pitch steps, c) quarter-tone pitch steps, d) eighth-tone pitch steps [hardest].

TESTING METHODOLOGY

The following is an outline of how MacCAD would be used in a typical test session, with details illustrating program components and features.

1. After seeing the initial screen, and the main menu (Fig. 1), the tester chooses the option "Learn to do it" and runs a "practice block" to familiarize client with the test format: "Click on the top button to hear the sound, then click on one of the bottom buttons to label the sound" (cards in this block are shown in Figs. 2a and 2b);

2. The tester chooses a sound set for testing, and shows the client how each item in the set is matched to each response button using a "look and listen" feature;

3. Tester then selects the parameters for a test condition (e.g., synthetic syllables "ba, da, ga" randomly presented to the right ear, for a total of 12 trials);

4. Control is then turned over to the client, who progresses through the sequence of trials at her/his own speed, clicking a button each time to hear the sound, then clicking on one of the label buttons to record the response (see Fig. 3 for example of a card for trials representing syllables, or tone patterns);

5. Feedback is displayed throughout: on each trial, as to whether the answer is right or wrong, and a total score at the end of a block of trials (see first panel in Fig. 4 for example of a final-score card) [every trial's sound and response are recorded automatically as testing proceeds];

6. At end of the block, tester takes control again, with options to either do on-line

analysis of the results (examples of analysis options in Fig. 4), select a new test condition, or exit.

PROGRAM EVALUATION: FIELD-TEST PROJECT

In order to demonstrate the sensitivity of MacCAD to a variety of disorders which may affect the auditory CNS, a field-testing pilot project was designed, in which representatives from several populations were to be tested on a battery including MacCAD. Components of the battery, and personnel responsible for each component are as follows:

1. MacCAD (2 sound sets: synthetic syllables, three-tone patterns). *Judith Lauter & Nancy Solomon* (Nancy is a doctoral student in the Speech & Hearing Sciences program at U of A)
2. audiometric tests (pure-tone audiogram, immittance if indicated by PT audiogram, subset of Synthetic Sentence Identification test [a conventional CAD test]) *Colette Coe* (Colette is a master's student in Speech & Hearing Sciences at U of A)
3. Repeated Evoked Potentials/Auditory Brainstem Responses (REPs/ABRs) session, modelled on our work with normal young adults as well as individuals with multiple sclerosis (see references), including repeated-measures testing of left, right, and binaural conditions. *Janiece Lord-Maes* (Jan is a post-doctoral assistant for our Coordinated Noninvasive Studies (CNS) Project).

Subject groups to be tested (target is 3 representatives of each of the first 4 categories, plus matched normals, for a total of 24 subjects) include:

1. "central auditory disorders" [clinical diagnosis]
2. multiple sclerosis [pre-selected to have positive REP/ABR signs of brainstem involvement]
3. Parkinsonism
4. sensorineural hearing loss
5. normals [for the pilot, at least one normal age-match for each of the above individuals]

For this report, data for six individuals will be described: two diagnosed as CAD, 1 elderly, 2 Parkinson's, and 1 MS. (Data are presented in Figs. 5-10.)

1. MAB [Fig. 5] (27, male, CAD; personal right-sided, familial right-sided "pRfR", and no known twins on either mother's or father's side): normal audiometric results, including pure-tone thresholds, word-recognition, impedance and acoustic

reflexes, and scores on SSI test; configuration of "relative ear advantages" is opposite what would be predicted based on his sidedness characteristics, i.e., the EA for syllables is to the left of that for the tone patterns; a possible clue to this is the very low score in the right ear for the syllables. In the companion paper, we will look for a physiological correlate of this finding in his REP/ABR data.

2. SHB [Fig. 6] (40, female, CAD; pRfR and no known twins): audiometrically normal including SSI scores; her EAs are dramatically polar opposites, in the direction predicted by her sidedness characteristic--very large REA for syllables, very large LEA for tone patterns; the sound x ear scores show this is is based on a "release from competition" pattern, which we have previously hypothesized would result from a breakdown in communication (including competition during dichotic presentation) between the cerebral hemispheres). REP/ABR: will the results of this test provide any support for this suggestion?

3. HCS [Fig. 7] (81, female, "central presbyacusis;" pRf? and no known twins; audiometrically appropriate for her age, with sloping SNHL above 1 kHz, but good word recognition and ceiling SSI scores): on MacCAD, she performed very well on both the "easy" syllable set (scores shown in the figure are for the ba/da/ba/ plus voiced set), and the tone patterns--illustrating the usefulness of the tone patterns (frequencies located within the spared portion of her audiogram) for evaluating central hearing in this age group; the small overall left ear advantage for both sound sets may be misleading, since for both sets, her right ear was learning throughout the procedure, perhaps indicative of a "slow rise time" in this age group, suggesting a second session tapping this "right-ear learning" would have yielded more "correct" EAs. REP/ABR: physiological data may help determine whether this hypothesis, i.e., that her right ear may in the long run prove more capable than is represented in these scores, has any physiological basis.

4. FFF [Fig. 8] (55, male, mild Parkinson's, pRfL and twins on mother's side; audiometry appropriate for age, with a mild SNHL deficit starting at 4 kHz, and ceiling SSI scores; the most interesting feature of his clinical presentation was the self report of a right-ear hearing loss which was not reflected in the audiometry): the predicted relative EA configuration for his sidedness profile would have the syllable EA to the left of the tones EA, but the sounds currently available in MacCAD did not allow us to support this prediction (another step in difficulty for the tones is needed, plus an intermediate level of difficulty for the syllables); there is no indication in the MacCAD performance regarding his self-reported right-ear hearing loss. REP/ABR: any support for his complaint?

5. MM [Fig. 9] (50, male, moderate Parkinson's, pRfR and no known twins; audiometrically normal for his age with some asymmetrical loss above 4kHz disfavoring the left ear and ceiling SSI scores): relative EAs are as predicted by

sidedness, with EA for syllables to the right of EA for tones; performance levels for all sound x ear combinations are good, and together with the audiometric findings indicate no central auditory dysfunction per se in this subject. REP/ABR: if the REP/ABR data suggest abnormalities, they may be of the nature observed in MS patients, i.e., reflective of brainstem integrity in general rather than indicative of specifically auditory problems.

6. KH [Fig. 10] (41, female, MS, pLfL with no twins on mother's side and uncertain on father's side; asymmetrical slight SNHL above 3 kHz disfavoring the left ear): as with MAB (subject #1 above) KH's relative EA pattern is opposite what would be predicted from her sidedness characteristics--here, we would expect the syllables would evoke an EA to the left of that for the tones; this reversal is accompanied by a symptom analogous to one shown by MAB, namely, an abnormally low score for one sound x ear combination: here, the left ear on syllables, which could account for the "released" (too-) large REA for the syllables in the face of a hypothesized underlying specialization which should favor left-ear performance on these sounds. REP/ABR: will her REP/ABR data show anything supporting this guess (analogous to what we will look for in MAB's physiological results)? [See companion paper for answers to all these REP/ABR questions.]

CONCLUSION

While the pilot results on representatives of patient groups are admittedly extremely preliminary, these findings suggest that, particularly in comparison with the audiometric findings, MacCAD dramatically increases the sensitivity and detail available from each subject regarding perception of complex sounds under complex (i.e., dichotic) presentation conditions.

Experience to date also indicatesa that both in terms of its test-design principles as well as program features, MacCAD is viable for use with a variety of clients, providing sensitivity and customization packaged in a form which is easily learned by the tester, and readily accepted by clients because of the graphic interface and self-pacing features. Subjects clearly have the impression that they are "self-administering" the test, rather than being passively given a test by someone else.

A video tape of one session with an older lady who had never used a computer before (much less a Macintosh and a mouse!) demonstrates her delight in learning to interact with the graphic, responsive screen with its easy-to-read labels and helpful feedback. The session is highlighted by one point when she cries out, "This is fun! I can see why kids like those video games!" In fact, the next step planned for MacCAD is to observe children's reaction to it, in order to determine what if any modifications will be needed to make this new clinical tool useful for an even wider age range, and thus extend its potential value.

THE FUTURE: POTENTIAL USES

MacCAD was designed to be useful for a variety of populations, from children to oldsters, from computer-phobes to computer-philes. Certainly, given the user-friendly Mac environment, testers would not have to know much about computers to use it, and the program is designed to be as learnable as possible, with easy start-up, straightforward principles of testing and analysis, and simple access to new sound sets and versions of sets. The current version requires a Mac with stereo play and is best if run on a fast-chip machine: thus a minimum system is an SE/30. This should be within the budgets of schools and public clinics, and could make the program with its state-of-the-art psychoacoustic design accessible for quite modest environments.

Certainly central testing, if it can be incorporated in such an easy-to-use, easy-to-expand format, has a wide range of predictable potential applications, in children with learning disorders, "central" young adults, individuals with organic or traumatic brain damage (aphasia, etc.), presbyacusics, as well as populations who might have "silent" auditory dysfunction, including individuals with Alzheimer's Disease, Parkinsonism, multiple sclerosis, etc.

A friendly, powerful program like MacCAD, particularly when combined in a battery with other tests such as standard audiometry and the individually-sensitive REPs/ABRs procedure (see companion paper), could potentially expand the audiologist's client population dramatically, opening a new diagnostic window for these professionals onto what many see as their natural future, evaluation of auditory sequelae of disorders affecting the central nervous system.

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(1)

MacCAD
Central Auditory Diagnostics for the Macintosh

Judith L. Lauter, Ph.D.
Version 1.0 Nov. 1990

This program was developed under a grant from the American Speech-Language-Hearing Foundation and Apple Computer, Inc., Community Affairs

Test selection

Data files

(2a)

For this test, you click on a button to hear a sound ---

(try clicking on this button)

Play boing

Easy? Then you will have other buttons to click to label the sound you heard.....

Go on

MAIN MENU

Please proceed in order, starting with "Listen to sound set"

Listen to sound set

You are here

Analyze data

Learn to do it

Load sound for test

Monaural test

Dichotic test

Exit

They will be larger buttons, like these:

Click the one you think is right.....

"boing"

mockingbird

Beethoven

then click here to go on.

26

They will be larger buttons, like these:

Click the one you think is right.....

"boing" | mockingbird | Beethoven

Thanks -- that's the right answer !

3

LEFT ear

Let's go!!

Ba | Da | Ga

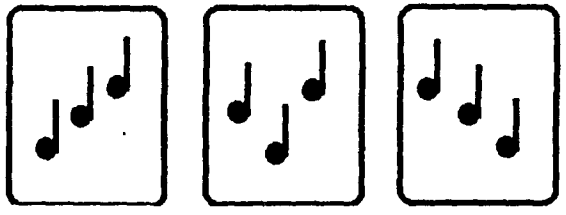
1

Ready to try it? Remember, when you see a new card, click on the top button to hear the sound,
then click on one of the 3 big buttons to record your answer.

Let's go!

LEFT ear

Let's go!!



1

That's the end of the block.

Your score is: 75 % correct.

Tell the tester you're done, and thank you for listening so carefully!

Options

The confusion matrix for this block is:

Responses> Stimuli v	Ba	Da	Ga	SubTot
Ba	2	2	0	4
Da	2	2	0	4
Ga	0	0	4	4
SubTot	4	4	4	12

Grand Total

For more results:

go Selection

To quit without saving:

go to main menu

JLL

10/22/90
7:30 PM

Real stops voiced
Monaural
Left
12

For more results or to save:

go Selection

To run another block without saving results:

Trial/stimulus/response:

1,3,2
2,1,2
3,2,1
4,1,2
5,2,2
6,3,2
7,3,

Results

*****

Ba
Da
Ga

To quit without saving or testing:

go Main Menu

Percent correct scores for this block:

Ba	50 %
Da	50 %
Ga	100 %
Overall	66.666667 %

To run the same block again, same subject:

To save results:

go Selection

To print results:

go Print-out

To quit without saving:

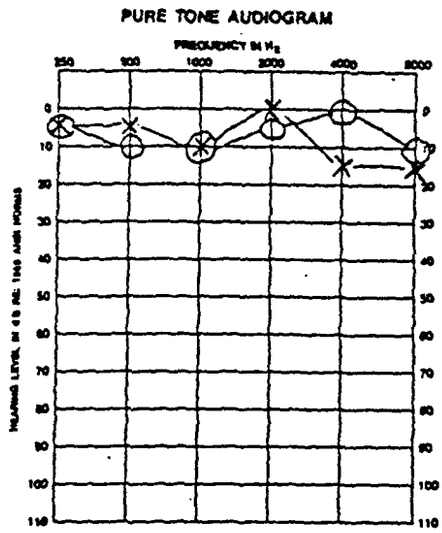
go Main Menu

Subject: MAB ♂ CAD
Age: 27
Sidedness: pRfR: no twins

Audiometry:

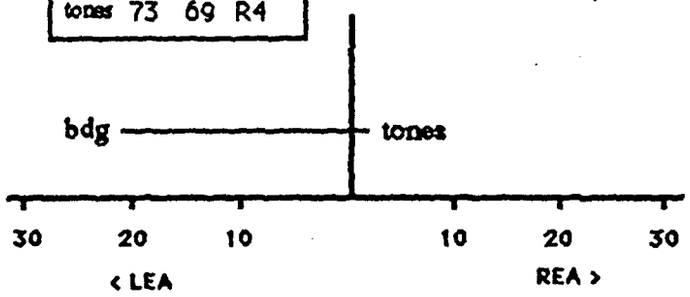
1. Pure-tone results normal bilaterally.
2. Word recognition ability excellent bilaterally.
3. Normal impedance findings and normal acoustic reflexes bilaterally.

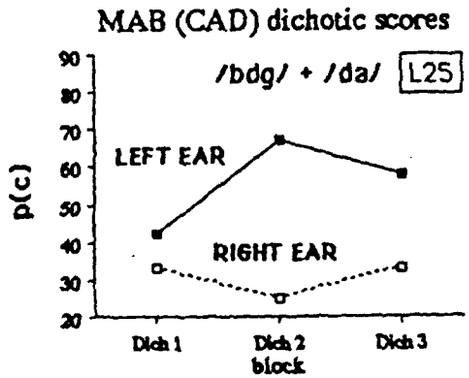
SSI: 100% Right, 87% Left

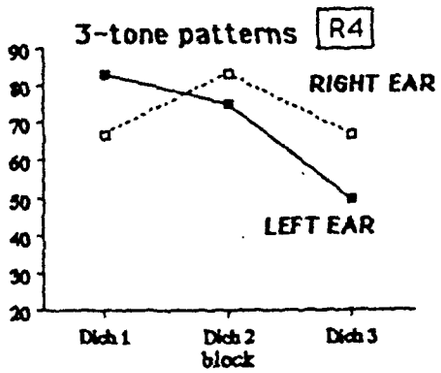


MacCAD:

scores:	R	L	EA
syll	31	56	L25
tones	73	69	R4

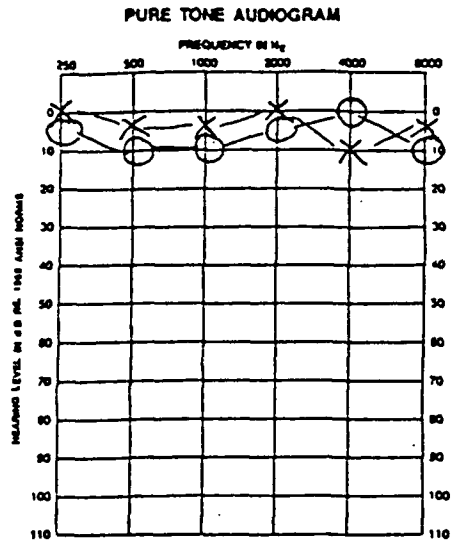






(6)

Subject: SHB ♀ CAD
Age: 40
Sidedness: pRfR; no twins



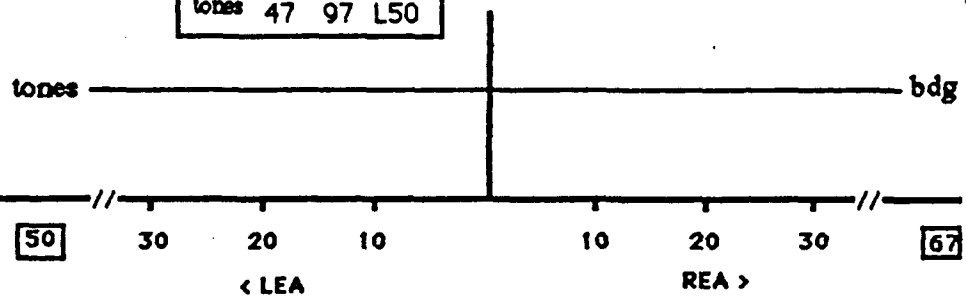
Audiometry:

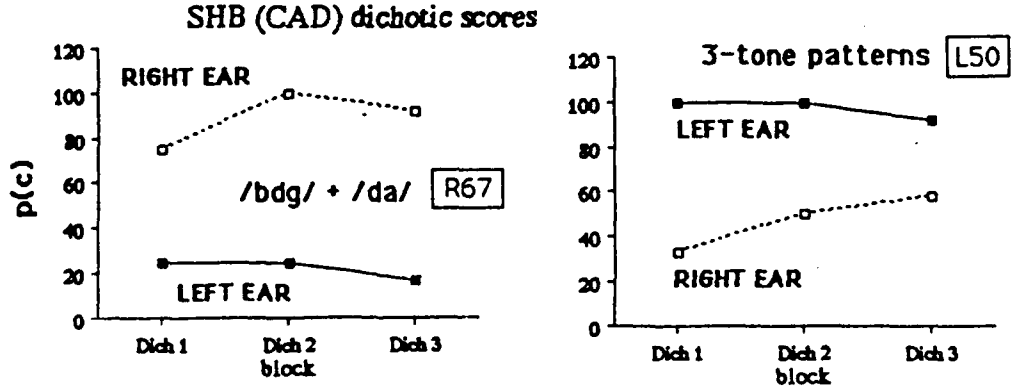
1. Pure tone audiometry normal for both ears, 250 - 8kHz.
2. Word recognition ability excellent bilaterally.
3. Impedance and reflexes normal in both ears.

SSI: 100% Right, 87% Left

MacCAD:

scores:	R	L	EA
syll	89	22	R67
tones	47	97	L50

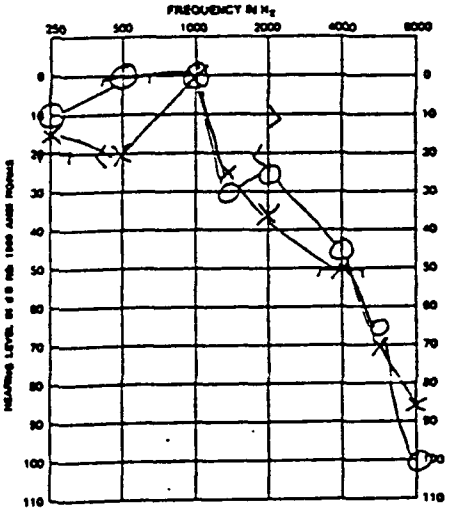




ELDERLY

Subject: HCS ♀
Age: 81
Sidedness: pRf?; no twins

PURE TONE AUDIOGRAM



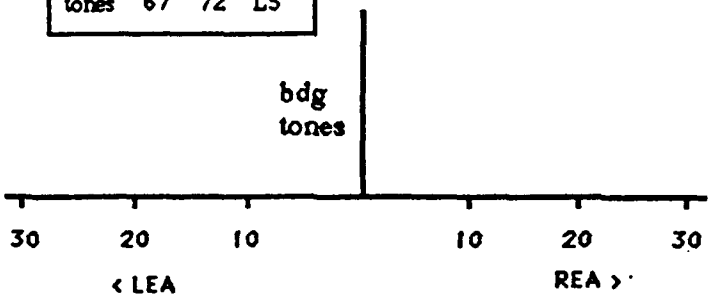
Audiometry:

1. Pure-tone air and bone conduction results indicate normal/ borderline sensitivity 250 - 1000 Hz, sloping from mild to severe/profound at 2K - 8K (SNHL).
2. Word recognition ability excellent bilaterally.
3. Impedance normal in R. with normal acoustic reflexes; could not obtain a seal on the L ear for impedance testing.

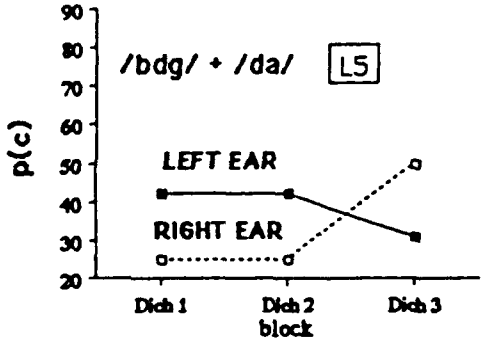
SSI: 100% Right, 87% Left

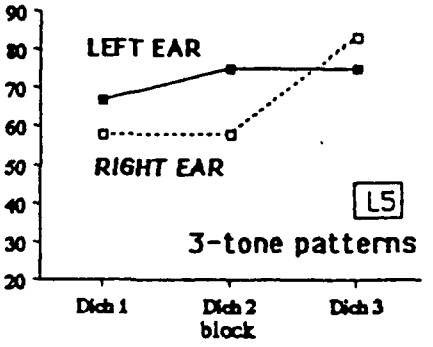
MacCAD:

scores:	R	L	EA
syll	33	38	L5
tones	67	72	L5



HCS (81 yrs) dichotic scores





Subject: FFF ♂

Age: 55

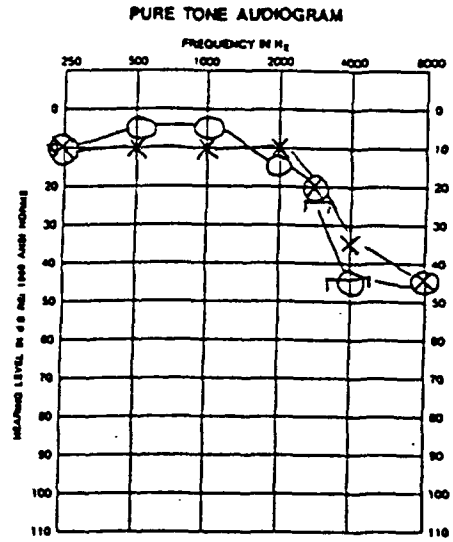
Sidedness: pRfL (1 brother); twins on mother's side

PARKINSON'S DISEASE

Audiometry:

1. Pure-tone results normal bilaterally through 3 kHz, with mild SNHL deficit 4-8kHz bilaterally.
2. Word recognition ability excellent bilaterally.
3. No tip big enough to seal for impedance or reflex testing.

[Self-report: some hearing loss in the Right ear]

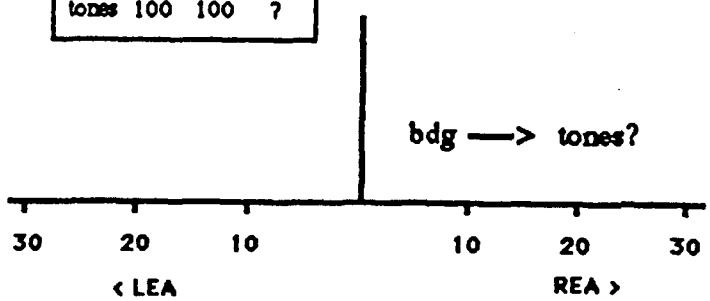


SSI: 100% both ears

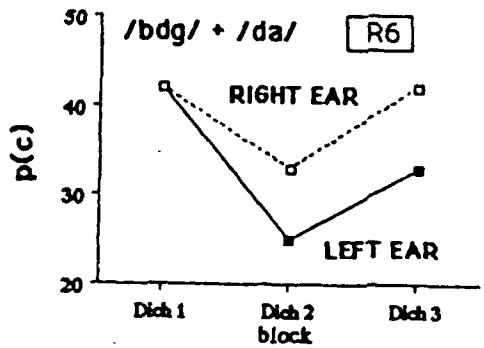
MacCAD:

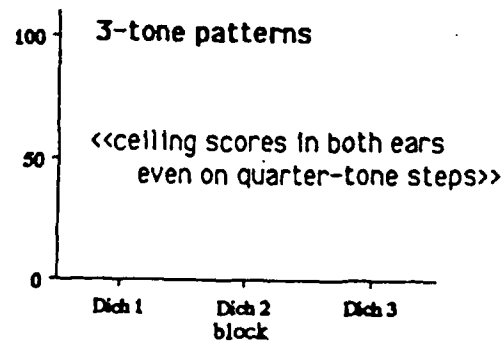
scores:	R	L	EA
syll	39	33	R6*
tones	100	100	?

*100% both ears on easy set



FFF (Parkinson's) dichotic scores





PARKINSON'S DISEASE

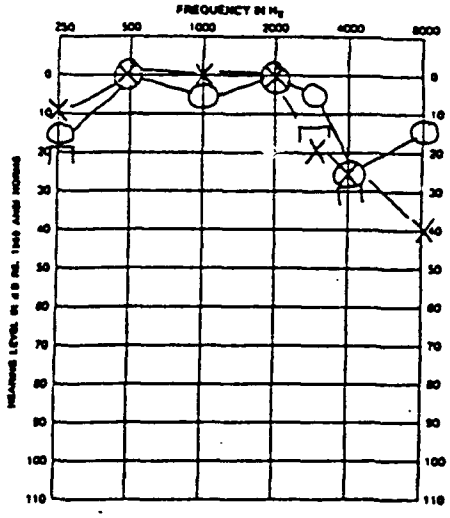
Subject: MM ♂
Age: 50
Sidedness: pRfR; no twins

Audiometry:

1. Pure-tone results normal bilaterally through 3kHz, slight deficit in R at 4 kHz, and mild deficit 4K-8K in L.
2. Word recognition ability excellent bilaterally.
3. Normal impedance findings and normal acoustic reflexes bilaterally.

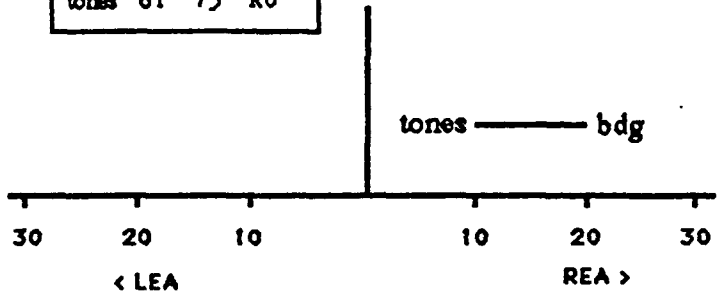
SSI: 100% both ears

PURE TONE AUDIOGRAM

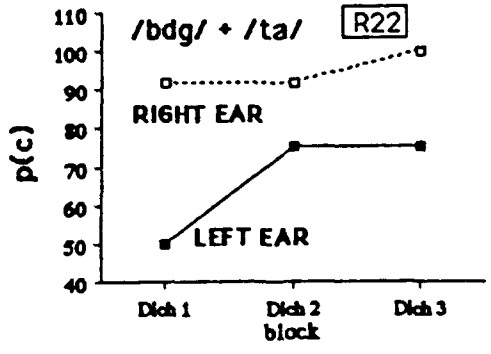


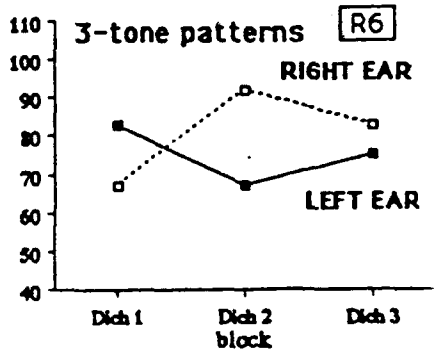
MacCAD:

scores:	R	L	EA
syll	97	75	R22
tones	81	75	R6



MM (Parkinson's) dichotic scores





(10)

Subject: KH ♀ MULTIPLE SCLEROSIS

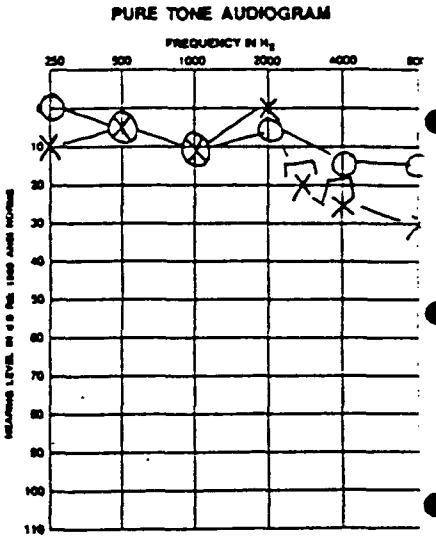
Age: 41

Sidedness: pLfL; no twins mother's side (father's?)

Audiometry:

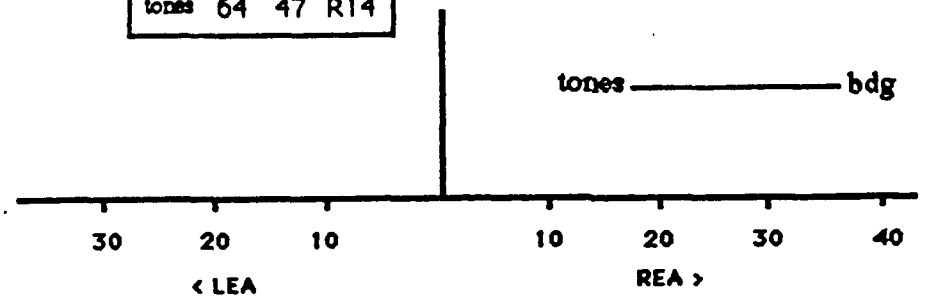
1. Hearing sensitivity within normal limits for the right ear and normal through 2 kHz in the left ear with a slight SNHL at 3 kHz - 8 kHz.
2. Word recognition ability excellent bilaterally.
3. Impedance and reflexes normal in both ears.

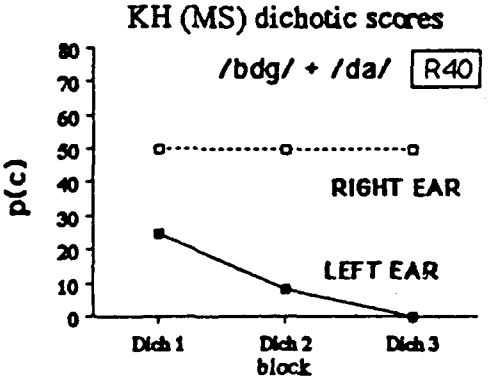
SSI: 100% Right, 100% Left

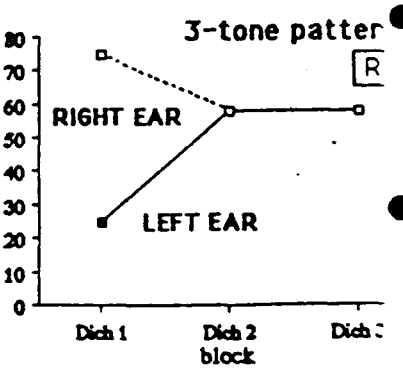


MacCAD:

scores:	R	L	EA
syll	50	11	R40
tones	64	47	R14







MacCAD and REP/ABRs: a new test battery for central auditory dysfunction. *Judith L. Lauter and Janiece Lord-Maes (Dept. of Speech and Hearing Sciences, University of Arizona, Tucson, AZ 85721). [Abstract: J Acoust Soc Amer (1991) 89: 1975]

ABSTRACT

Traditionally audiologists have specialized in the peripheral hearing system. However, recent advances in the diagnosis and treatment of peripheral problems, together with developments in brain imaging, suggest that the future of audiology is in the brain, focusing on dysfunctions resulting from CNS pathology. Financial realities dictate that the first steps toward this new future emphasize technologies which are already available and/or reasonably priced. Two components of a test battery based on these principles have been developed in our laboratories. A companion paper describes MacCAD, a Macintosh-based program for monaural/dichotic testing of speech and nonspeech sounds, which can be run on a Macintosh SE/30 with no additional hardware. Second, a simple repeated-measures modification of evoked-potential testing (Repeated Evoked Potentials [REPs]) applied to auditory brainstem responses (ABRs) yields a dramatic increase in sensitivity to individual characteristics, based on standard EP equipment and procedures. Pilot testing with a combination of these two tests suggests that the two-part battery is not only sensitive to individual characteristics of central auditory function, but may also reveal striking correlations between the results on each test, such that details of an individual's performance on one may predict specific details observed with the other. Thus the combination of the two tests can provide complementary behavioral/physiological documentation of underlying dysfunction which may be invisible to conventional testing. In those cases where testing is available on more expensive brain-monitoring tools such as MRI, qEEG, and PET, this battery could also serve as a basis for hypothesis formulation, thus rendering their use more cost-effective.

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INTRODUCTION

In a series of presentations and papers (see references) we have described the results of a simple repeated-measures modification to standard ABR testing procedures, which yields a dramatic increase in sensivity to individual

characteristics over conventional EP analysis procedures. The first clinical test of this approach was reported for a group of MS patients, to the fall 1990 meeting of this Society (Lauter & Lord-Maes 1990), and the results encouraged us to pursue preliminary testing in other groups of individuals who might be expected to present with involvement of central auditory pathways.

The companion paper (Lauter, Solomon, and Coe 1991) describes initial behavioral testing of six such subjects, including a standard audiometric battery combined with collection of relative ear advantages (see description in that paper) for two sound sets-- synthetic syllables, and three-tone patterns based on 200-ms inter-onset-interval timing. As that paper describes, the EAs were collected with MacCAD, a new program in Hypercard developed in our laboratories for the Macintosh SE/30 and Mac II series.

The current paper will add the REP/ABR data for each subject to these findings, to yield complete reports for each individual (Figs. 1-6). Discussion of the results below is by subject, and focuses on descriptions of connections between the behavioral and physiological findings (for more complete treatment of the behavioral findings alluded to here, and summarized in the figures, see the companion paper).

METHODS

Each subject was scheduled for a single REPs/ABR session, lasting approximately 1.5 hours. In each session, four 2000-sweep ABRs were collected for each of left-ear, right-ear, and binaural stimulation, using procedures described previously (see references) based on standard clinical protocols. At the end of the session, an additional four binaural waveforms were collected from each subject. Only the monaural data will be described here.

Mean latency and amplitude were calculated for each of the first five vertex-positive peaks for each ear condition in each subject, along with the standard deviation of these parameters. As described in our previous reports, the ratio of mean divided by standard deviation (the "Coefficient of Stability") was calculated for each peak x ear combination to yield data for plotting "stability profiles," describing the relative latency and amplitude stability for each peak x ear condition in each subject.

Then each subject's complete data set (mean latency and amplitude, latency and ampitude stability, for five peaks under three ear conditions) was compared with analogous values from a database of normal adults (age range 20-50). The number of instances of deviation from the normal values (equal to or beyond 1 standard deviation, equal to or beyond 3 standard deviations) was tabulated for each peak x ear condition for each subject, and summarized in a "REP score profile," such as

those shown for left and right ears for subject MAB at the bottom of Fig. 1.

In these graphs, those instances where the subject's values were earlier (in latency) or higher (in amplitude, or either type of stability) than normal are plotted with positive-going dotted bars, and categorized as "early/high scores." Those instances where the subject's values were later (in latency) or lower (in amplitude, or either type of stability) than normal are plotted with negative-going solid bars, and categorized as "late/low scores." Thus MAB's left ear is characterized as having a REP score total of "2 late/low, 6 early/high," and his right ear has a REP score total of "4 late/low, 8 early/high." This scoring procedure was first described in Lauter & Lord-Maes (1990). Based on previous experience we have hypothesized that late/low scores are indicative of problems within the brainstem itself, while early/high scores may suggest dysfunction affecting supra-midbrain structures, including the cortex.

1. MAB [Fig. 1]: ABR data for both of MAB's monaural conditions indicate abnormalities, both according to conventional analysis (comparisons of latency intervals and amplitude ratios-- indicated here by the asterisks), as well as in terms of the REP-score comparisons of absolute and stability measures with our normal database. More specifically, the striking abnormality in MAB's MacCAD results discussed in the companion paper (i.e., the very low score for right-ear attention to syllables) may have a physiological correlate in the REP-score values for right-ear peak IV, where both mean amplitude as well as amplitude stability are more than 3 sd higher than normal.

While it is possible that this unusual finding points to a dysfunctional characteristic within the right-ear pathways of the brainstem, it may also be indicative of a problem in the left hemisphere, such that the brainstem response to the right-ear input is "released" from corticofugal modulation, resulting in abnormally large and abnormally stable amplitude of peak IV. This latter hypothesis regarding a "release" effect is based on our previous REP/ABR findings in MS patients, combined with observations of brainstem "hyper-responses" in individuals with a history of hyperactivity and substance abuse. Further testing of MAB, with qEEG and MRI (and ideally with PET and MEG) could corroborate the suggestion in these combined MacCAD + REP/ABR data of a cortical dysfunction which might be the source of his complaints of problems with everyday listening tasks.

2. SHB [Fig. 2]: Conventional analysis of ABR abnormalities revealed no problems in this subject's waveforms (no asterisks here), but the REP scores indicate a number of instances of "early/high" scores, suggesting, as hypothesized for MAB above, cortical dysfunction resulting in a release effect on brainstem response. The effect appears in both ears, corroborating our hypothesis in the companion paper that SHB's exaggerated EA values, based on reciprocal ceiling/floor

combinations of sound x ear scores, may be due to problems in the cerebral hemispheres, either involving areas in each hemisphere separately, or a breakdown in interhemispheric connections. Again, the agreement between the MacCAD data and the REP/ABR signs indicate the usefulness of combining these two tests as a battery, and combines to generate specific hypotheses for further testing, in this case, exploring the possibility of cortical dysfunction.

3. HCS [Fig. 3]: This elderly subject has an abnormal left-ear ABR according to conventional analysis (prolonged I-III and I-V latency intervals both due to an abnormally early peak I, compared with younger adults), and this problem with her left ear may account for the rather complicated picture of attended-ear scores seen in the MacCAD data. Although the right ear does show some REP-score abnormalities, these are more evenly distributed across peaks than in the left, and are also combined with fewer of the "early/high" scores than is true for the left. The slowly improving right-ear performance seen in the MacCAD testing chronology may be accounted for by: a) co-occurring problems in both ears, which is perhaps typical of this age group, combined with b) more problems in the left than in the right, an asymmetry which over time allows the right ear to slowly gain ascendancy in testing with both sound sets (see companion paper for related figure).

Also, the combination of early/high and late/low scores seen in both ears for this elderly subject suggests a mixture of supra-midbrain plus brainstem dysfunction, which would be expected for this age group-- as well as for individuals with distributed effects of degenerative diseases, such as multiple sclerosis (see discussion for subject KH, #6 below).

4. FFF [Fig. 4]: As noted in the companion paper, this subject with mild Parkinson's Disease seemed to perform normally and very well on all tests, audiometric as well as MacCAD. The primary puzzle for him was his self-reported right-ear hearing loss which was not supported by any of the behavioral tests. However, note that the REP-score profiles suggest a possible concomitant of this impression, in that while the score totals for the two ears are similar (9LL, 1EH for the left vs. 11 LL, 0 EH for the right), the right-ear response has a predominance of low scores at early peaks (6/11 occur at peaks I and II), while low scores for the left occur at peak III and later. Further testing is clearly needed to determine whether this suggested relation between distribution of late/low REP scores and subjective impressions of hearing loss is observed in other individuals.

5. MM [Fig. 5]: The REP-score profiles for MM's monaural conditions may be correlated with his somewhat more advanced Parkinson's stage compared with FF, in that MM has two instances of response hyperstability (abnormally high latency

stability at peak III in the left-ear response, and abnormally high amplitude stability at peak II in the right). The clear asymmetry in REP scores, twice as many low scores for the right-ear than for the left-ear response, suggests a unilateral effect often characteristic of Parkinson's, an effect which in this case is in fact in the direction which would be predicted by the unilateral motor effects observed in this individual, thus supporting the REP score as an index of CNS functional integrity.

6. KH [Fig. 6]: This moderately-severe MS patient's paradoxical relative EA scores (EA for syllables to the right of EA for tones, although she is familial left-sided) may be accounted for by the variety of problems suggested in the REP-score profiles for both ears. By conventional analysis, both left-ear and right-ear responses have abnormal amplitude ratios and/or latency intervals, and the REP profiles reveal a mixture of early/high (hypothesized supra-midbrain dysfunction) and late/low (brainstem dysfunction) scores. The "drop-out" score in her MacCAD matrix (left-attended for syllables) may be related to the multiple low REP scores at left-ear-response peaks IV and V: it is possible that with this much dysfunction at the level of the upper pons and midbrain (?), not enough signal characteristics are transmitted to the right hemisphere (hypothesized to be the site of stop-CV processing in this pLfL individual) to enable accurate identification of synthetic stops-- although enough can get through to yield higher scores for the tone patterns, which are of course characterized by a very different set of dimensional values (see Lauter 1982, 1983, 1984 for a discussion of the influence of stimulus characteristics on EAs).

CONCLUSION

Data sets similar to those discussed above have been collected for one additional Parkinson's patient, three more MS individuals, and an additional elderly subject. Analysis of those results will indicate whether the very preliminary suggestions made here are supported or whether they are in need of revision.

Continued testing of other normals, additional subjects from the same populations represented here, as well as new patient groups, can be expected to lead to modifications in MacCAD as well as in our interpretation of MacCAD and REP results. However, we believe that the initial indications of logical relations which we have described here, between the behavioral details provided by MacCAD and the physiological sensitivity of the REP protocol, promise new insights into both normal and disordered function of the central auditory nervous system. It is hoped that further test development and exploration along these same lines may lead to new and more powerful tools for the "central audiology" of the future.

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(1)

Subject: MAB ♂ CAD
Age: 27
Sidedness: pRfR; no twins

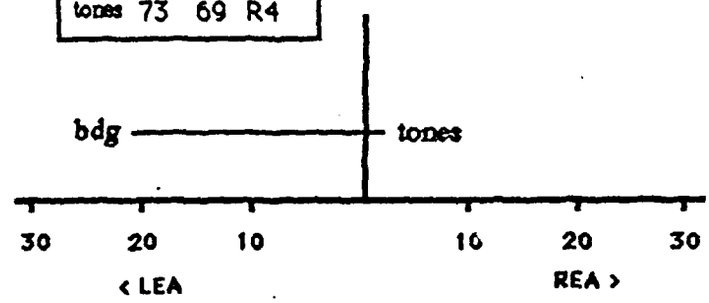
Audiometry:

1. Pure-tone results normal bilaterally.
2. Word recognition ability excellent bilaterally.
3. Normal impedance findings and normal acoustic reflexes bilaterally.

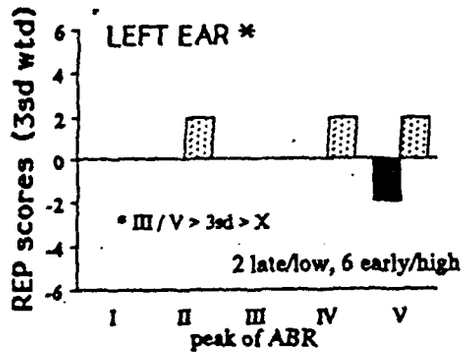
SSI: 100% Right, 87% Left

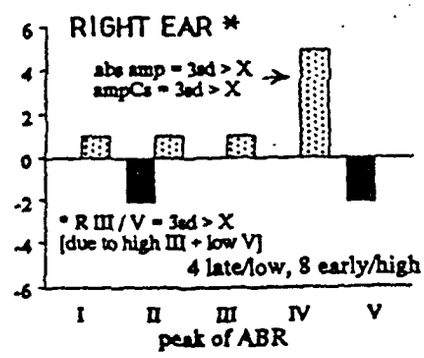
MacCAD:

scores:	R	L	EA
syll	31	56	L25
tones	73	69	R4



REP/ABR:





(2)

Subject: SHB ♀ CAD
Age: 40
Sidedness: pRfR; no twins

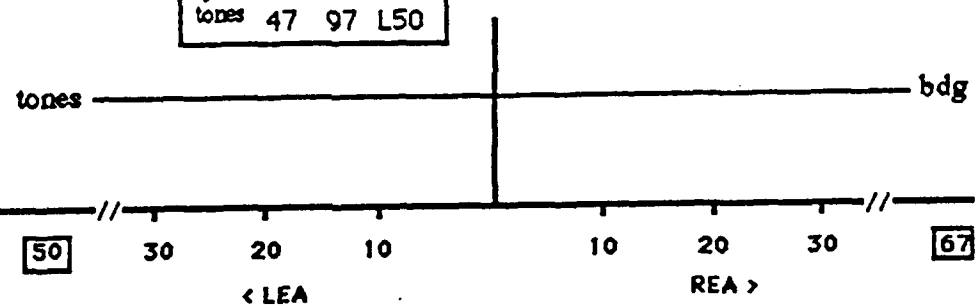
Audiometry:

1. Pure tone audiometry normal for both ears. 250 - 8kHz.
2. Word recognition ability excellent bilaterally.
3. Impedance and reflexes normal in both ears.

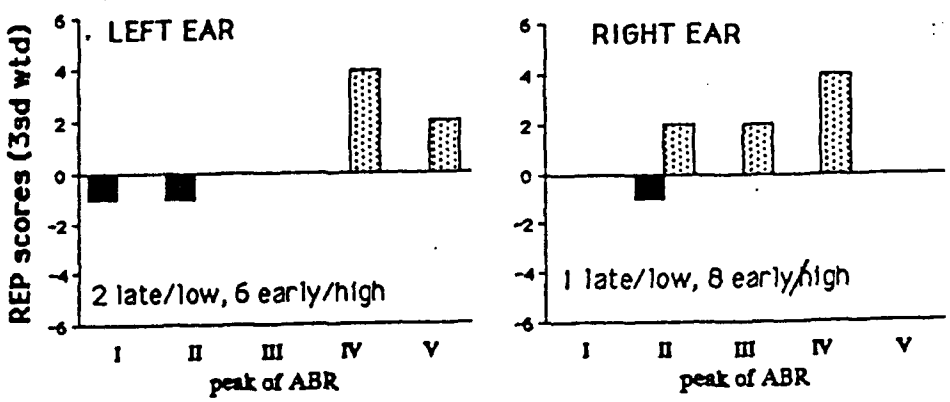
SSI: 100% Right, 87% Left

MacCAD:

	scores:		
	R	L	EA
syll	89	22	R67
tones	47	97	L50



REP/ABR:



(3)

ELDERLY

Subject: HCS ♀
Age: 81
Sidedness: pRf?; no twins

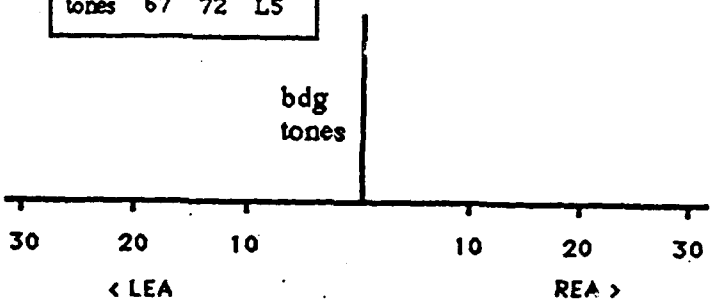
Audiometry:

1. Pure-tone air and bone conduction results indicate normal/ borderline sensitivity 250 - 1000 Hz. sloping from mild to severe/profound at 2K - 8K (SNHL).
2. Word recognition ability excellent bilaterally.
3. Impedance normal in R. with normal acoustic reflexes; could not obtain a seal on the L ear for impedance testing.

SSI: 100% Right, 87% Left

MacCAD:

scores:	R	L	EA
syll	33	38	L5
tones	67	72	L5



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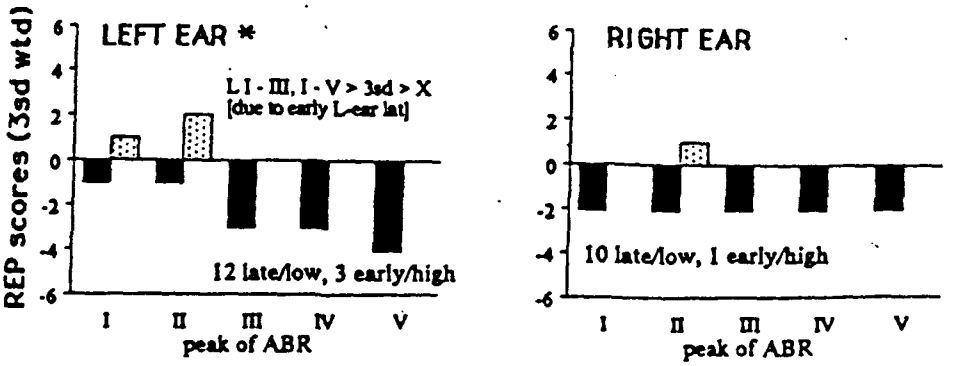


(4)

Subject: FFF ♂ PARKINSON'S DISEASE
Age: 55
Sidedness: pRfL (1 brother); twins on mother's side

Audiometry:

1. Pure-tone results normal bilaterally through 3 kHz, with mild SNHL deficit 4-8kHz bilaterally.
2. Word recognition ability excellent bilaterally.
3. No tip big enough to seal for impedance or reflex testing.

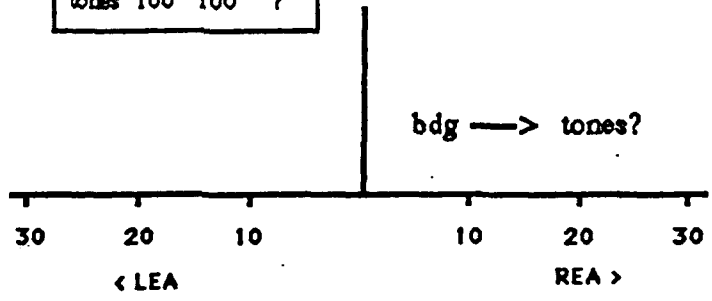
[Self-report: some hearing loss in the Right ear]

SSI: 100% both ears

MacCAD:

scores:	R	L	EA
syll	39	33	R6*
tones	100	100	?

*100% both ears on easy set



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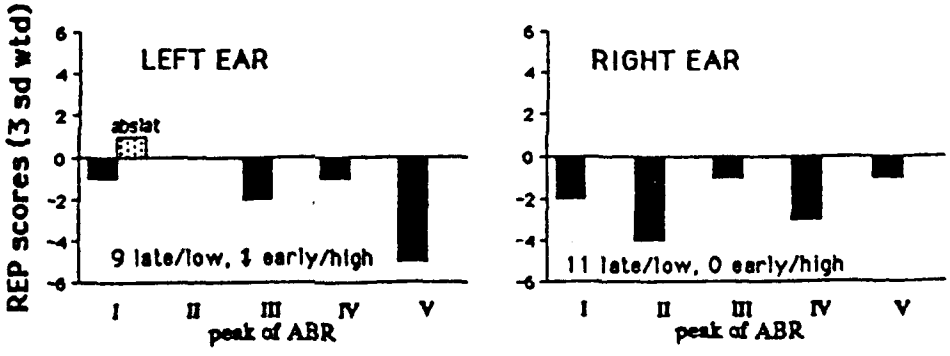


(5)

PARKINSON'S DISEASE

Subject: MM ♂
Age: 50
Sidedness: pRfR; no twins

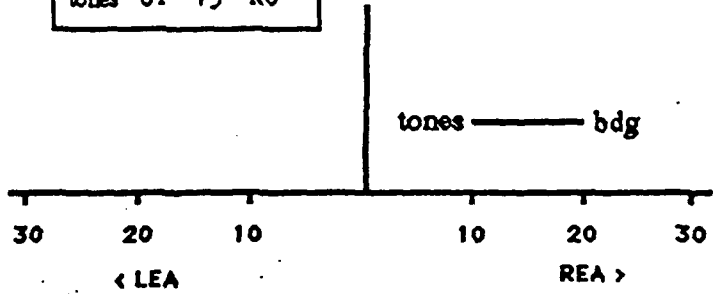
Audiometry:

1. Pure-tone results normal bilaterally through 3kHz, slight deficit in R at 4 kHz, and mild deficit 4K-8K in L.
2. Word recognition ability excellent bilaterally.
3. Normal impedance findings and normal acoustic reflexes bilaterally.

SSI: 100% both ears

MacCAD:

scores:	R	L	EA
syll	97	75	R22
tones	81	75	R6



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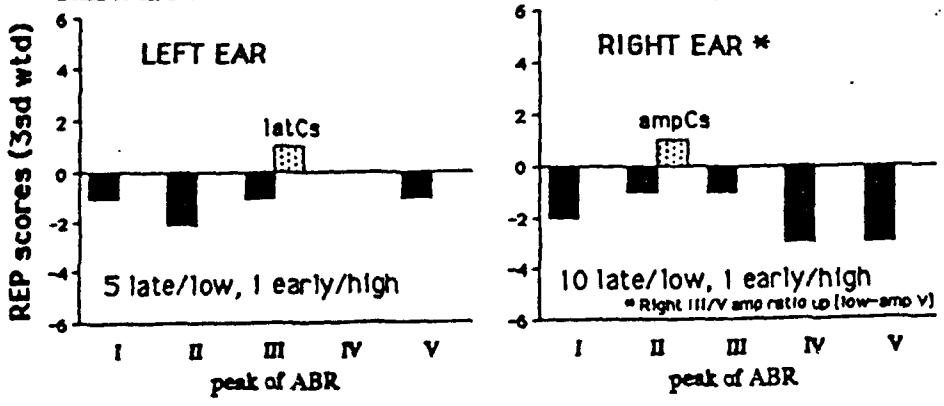


(6)

Subject: KH ♀ MULTIPLE SCLEROSIS
Age: 41
Sidedness: pLfL; no twins mother's side (father's?)

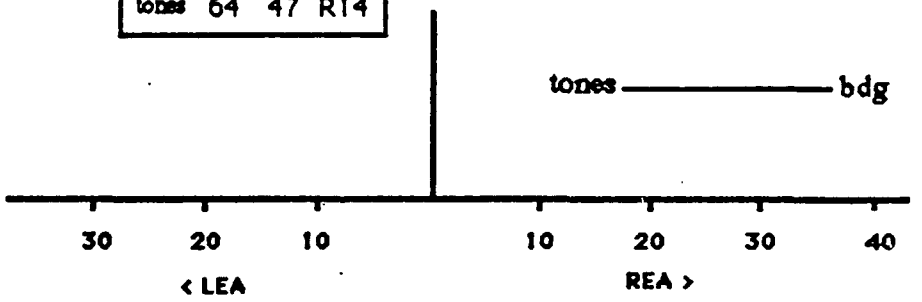
Audiometry:

1. Hearing sensitivity within normal limits for the right ear and normal through 2 kHz in the left ear with a slight SNHL at 3 kHz - 8 kHz.
2. Word recognition ability excellent bilaterally.
3. Impedance and reflexes normal in both ears.

SSI: 100% Right, 100% Left

MacCAD:

scores:	R	L	EA
syll	50	11	R40
tones	64	47	R14



REP/ABR: